

**UNIVERZITA KARLOVA V PRAZE,  
LÉKAŘSKÁ FAKULTA V HRADCI KRÁLOVÉ  
A  
FAKULTNÍ NEMOCNICE V HRADCI KRÁLOVÉ**

**IX. VĚDECKÁ KONFERENCE**

**P R O G R A M**



**25. ledna 2005**

**Velká posluchárna teoretických ústavů Lékařské fakulty UK,  
Šimkova 870, Hradec Králové**

## Program 9. vědecké konference (2004)

### IX. vědecká konference Lékařské fakulty a Fakultní nemocnice v Hradci Králové

25. ledna 2005 - velká posluchárna teoretických ústavů LF, Šimkova 870

Úterý 25. 1. 2005

11.00 - 11.15 Z a h á j e n í k o n f e r e n c e  
prof. MUDr. Vladimír Palička, CSc., děkan lékařské fakulty  
doc. MUDr. Leoš Heger, CSc., ředitel fakultní nemocnice

#### **Sekce I** prof. MUDr. Vladimír Geršl, CSc.

11.15 - 11.35 Závažná orgánová selhání: experimentální a klinické aspekty, možnosti prevence a terapeutického ovlivnění  
koordinátor: [prof. MUDr. RNDr. Miroslav Červinka, CSc.](#)  
Výzkumný záměr MSM 111500001 (LF)

11.35 - 11.55 Hepatologie - fyziologické, patofyziologické a klinické aspekty  
koordinátor: [doc. MUDr. Zuzana Červinková, CSc.](#)  
Výzkumný záměr MSM 111500003 (LF)

11.55 - 12.15 Patogeneze, diagnostika a terapie nádorových onemocnění  
koordinátor: [prof. MUDr. Jaroslav Malý, CSc.](#)  
Výzkumný záměr MSM 111500002 (LF)

12.15 - 12.55 P ř e s t á v k a - občerstvení

#### **Sekce II** prof. RNDr. Jan Krejsek, CSc.

13.00 - 13.15 Proteomové centrum pro studium intracelulárního parazitismu bakterií  
[prof. MUDr. RNDr. Miroslav Červinka, CSc.](#)  
(nositel: Vojenská lékařská akademie JEP, Hradec Králové, odp. řešitel: doc. MUDr. Jiří Stulík, CSc.)  
Výzkumná centra LN00-A033 (LF)

13.15 - 13.30 Populační modelování chtěných a nechtěných klinických výstupů a náhradních parametrů  
[prof. MUDr. Jiřina Martínková, CSc.](#)  
COST OC B15.10 (LF)

13.30 - 13.45 Modelování kinetiky a dynamiky léků při jejich vývoji. Metody in vitro a in vivo.  
[prof. MUDr. Jiřina Martínková, CSc.](#)  
COST OC B15.30 (LF)

13.45 - 14.00 Zavedení a využití systémů kultivace lidských hepatocytů pro hodnocení metabolismu léků in vitro  
[doc. MUDr. Jaroslav Mokřý, Ph.D.](#)  
COST OC B15.40 (LF)

14.00 - 14.15 Elektrofyziologické hodnocení věkově závislých změn zrakového vnímání člověka  
[doc. MUDr. Miroslav Kuba, CSc.](#)  
GA ČR 309/02/1134 (LF)

14.15 - 14.30 Biochemické markery zánětu ve vydechovaném vzduchu u dětských astmatiků jako nová metoda sledování kontroly astmatu a prostředek pro optimalizaci farmakoterapie  
[Ing. Jaroslav Chládek, Ph.D.](#)  
IGA MZ ČR NL/7024-3/02 (LF)

14.30 - 15.00 P ř e s t á v k a - občerstvení

#### **Sekce III** prof. MUDr. Pavel Rozsival, CSc.

- 15.00 - 15.15 Predikace, optimalizace a individualizace výsledku léčebné procedury při LDL-aféřeze - multivariantní model v prospektivní studii  
**prof. MUDr. Milan Bláha, CSc.**  
IGA MZ ČR NB/7006-3 (FN)
- 15.15 - 15.30 Aterogenní potenciál poruch metabolismu mastných kyselin a cholesterolu v procesu koronární aterogeneze u diabetu mellitu II. typu  
**prof. MUDr. Vladimír Bláha, CSc.**  
IGA MZ ČR NB/6999-3 (FN)
- 15.30 - 15.45 Sledování kvality péče o nemocné s mimonemocniční oběhovou zástavou ve východočeském regionu  
**doc. MUDr. Miloslav Pleskot, CSc.**  
IGA MZ ČR NO/7254-3 (FN)
- 15.45 - 16.00 Magnetická rezonance versus thaliová scintigrafie v detekci viabilního myokardu. Prospektivní srovnávací studie.  
**MUDr. Miroslav Solař**  
IGA MZ ČR NA/7248-3 (FN)
- 16.00 - 16.15 Efektivitu biventrikulární stimulace lze hodnotit změnami neinvazivně měřené pulzové amplitudy  
**MUDr. Miloslav Tauchman**  
IGA MZ ČR NA/7261-3 (FN)
- U k o n ě n í k o n f e r e n c e  
prof. MUDr. Vladimír Palička, CSc., děkan lékařské fakulty

**SOUHRNY VÝZKUMNÝCH ÚKOLŮ  
ŘEŠENÝCH NA LF UK A VE FN V HRADCI KRÁLOVÉ  
(ABECEDNĚ)**

**Title of the research project:**

HPLC diagnostics of congenital disorders of glycosylation (CDG)

**Grant Agency:** Charles University, FRVŠ**Project Number:** 1770/G3**Principal Researcher:** Ziad Albahri**Joint Researchers:** Eliška Marklová**Starting date:** 1. 1. 2004**Duration (years):** 1**Funds allocated for project - total in Czech crowns:** 166 000**Summary of 2004 results****Title of the presentation:** HPLC in the screening of defects of glycosylation**Authors:** Ziad Albahri, Eliška Marklová and Jaroslava Vávrová\*

Department of Pediatrics and \*Department of Biochemistry, Faculty of Medicine, Charles University, Hradec Králové

There is a need for a reference method in the CDG diagnostics to prove results of screening, based on immunologic detection of glycoforms of serum transferrin (Tf), separated by IEF.

We introduced a HPLC procedure, and described our experience with the method. Iron-saturated and delipidated samples are separated on MonoQ, or ResourceQ anion-exchange column, using linear salt gradient elution. Quantification relies on the selective absorbance of the iron-Tf complex. HPLC of Tf isoforms in CDG screening enables good separation and quantification of the four most important Tf isoforms in controls, and several hypoglycosylated fractions in CDG patients, provided that a HPLC system equipped with detector of high sensitivity is used (e.g. Shimadzu 10AVB); not all detectors are suitable for this specific procedure (e.g. Agilent 1090, or ECOM 2084, otherwise satisfactory in many applications).

Some pitfalls and drawbacks connected with supposedly simple HPLC procedure of Tf isoforms are summarized. In general, there are based on the 1) low molar absorbency despite high specificity of the iron-Tf complex at 460 nm, 2) low concentration of the typical carbohydrate deficient glycoforms in serum, 3) claim for spectrophotometric detector of good performance at 460 nm, and 4) low pressure limit for ion-exchange HPLC columns. The other inconveniences, such as 5) long time of analysis with gradient elution, and 6) high expanses of HPLC column may be compensated by the automation possibility, and by a choice from among comparatively good columns the more economic ResourceQ (for half a price of that of MonoQ), respectively. The lack of 7) a clearly defined CDT analyte group thus complicating all steps of the analysis, and 8) commercially available standard of Tf-glycoforms, are other problems.

Charles Univ. Grant Agency 85/2001/C/LFHK, and FRVS 1770/G3 supported this study.

***Address for correspondence:*** Eliška Marklová, Department of Paediatrics, Charles University in Prague, Faculty of Medicine in Hradec Králové, Šimkova 870, 500 38 Hradec Králové, CR.

**Title of the research project:** Ruber dam use implementation in preclinical dentistry.

**Grant Agency:** Ministry of Education

**Project Number:** 992/2004

**Principal Researcher:** Petr Bednář

**Joint Researchers:** Petr Závodský

**Starting date:** 1.1.2004

**Duration (years):** 1

**Funds allocated for project - total in Czech crowns:** 91000

**Summary of 2004 results**

**Title of the presentation:** Ruber dam use implementation in preclinical dentistry.

**Authors:** Petr Bednář, Petr Závodský

Fac. Med., Charles Univ., Hr. Králové: Dept. of Dentistry

Ultimate goal of modern dental treatment is to perform treatment with the highest possible succes rate. Manual skill, adequate knowledge and training are essential.

Contemporarry dentistry lays stress on treatment safety. One of the most popular and widely used item to achieve dry, sterile working field in maximal safety during treatment is rubber dam. In Czech Republic its use is very rare.

With new dental curriculum our students should be advanced from former dental students after their graduation. The aim is to work routinely with rubber dam during preclinical and clinical practices. The funds from agency were used to buy starting sets of rubber dam and other accessories to fully equip our offices for students to use rubber dam during each practices.

Project was supported by Ministry of Education, No 992/2004

**Address for correspondence:** P. Bednář, Dept. of Dentistry, Charles University in Prague, Faculty of Medicine and Teaching Hospital in Hradec Králové, Sokolská 581, 500 05 Hradec Králové, Czech Republic

**Title of the research project:** Prediction, optimization and individualisation of therapeutic procedure in LDL-apheresis - a multivariate model in a prospective study

**Grant Agency:** IGA MH CZ

**Project Number:** NB/7006-3

**Principal Researcher:** Milan Bláha

**Joint Researchers:** Zdeněk Zadák, Vladimír Bláha, Jaroslav Malý, Melanie Cermanová, Vladimír Mašín

**Starting date:** 1.1.2002

**Duration (years):** 3

**Funds allocated for project - total in Czech crowns:** 1482

#### **Summary of 2004 results**

**Title of the presentation:** Computer controlled prediction of the optimal therapeutic procedure during LDL apheresis suitable for routine clinical practice

**Authors:** Milan Blaha (1), Vladimír Masin (2), Pravoslav Stransky (2), Vladimír Blaha (3), Melanie Cermanova (1), Jaroslav Malý (1), Martin Blazek (1), Zdeněk Zadák (3)

Fac. Med. and Fac. Hospital, Charles Univ., Hr. Králové: IInd Internal Clinic (1), Dpt. of Biophysics (2), Clinic of gerontology and metabolism (3)

LDL - apheresis is a very effective method in the treatment of resistant hypercholesterolemia when other therapy (dietary, medicamentous) fails. To maximize efficacy of the usage of LDL-absorbers we aimed to create a computerized model.

**Patients and methods:** The therapeutic technique was used of immunoabsorption, applying a pair of columns Lipopak®, Pocard, Russia. Plasma was separated by continuous-flow plasma separator Cobe Spectra, USA; adsorption was controlled by adsorption-desorption equipment ADA, Medicap, Germany. Repeated 494 LDL-apheresis procedures (treatment interval 17,5 + 1,6 days) has been used to treat nine patients with primary hypercholesterolemia followed over 3,6 + 0,5 consecutive years. Metabolism of the LDL-cholesterol is known to be multi-compartmental and dynamic, but in the short-time range of the procedure it can be simplified and the procedure can be assumed to be a continuous filtration. We developed a program for procedure planning, using Microsoft® Excel for Windows. Inputs into the program include only basic patient data (mass, height, sex and initial plasma LDL level in mmol/L).

**Results:** The results show a very promising match between our planning of the procedures and the real laboratory results. Calculated and real plasma LDL-cholesterol level drops differ no more than + 10 %; level of LDL dropped 17,7% more in the same time.

**Conclusions:** Although our software does not take into account many well known details concerning the metabolism of cholesterol, in given conditions it can provide a fairly precise prediction of procedure parameters. It is also suitable for practical use, because it requires only a few commonly used and readily available input values.

**Address for correspondence:** M. Bláha, Faculty Hospital, IInd Internal Clinic, Sokolská 486, 500 05 Hradec Králové, CZ





**Title of the research project:** Atherogenic role of disorders of fatty acid and cholesterol metabolism in coronary atherogenesis in diabetes mellitus type II

**Grant Agency:** Ministry of Health

**Project Number:** NB/6999-3

**Principal Researcher:** Vladimír Bláha

**Joint Researchers:** Dušan Černohorský, Dagmar Solichová, Petr Žďánský, Pavel Vyroubal, Radomír Hyšpler, Zdeněk Zadák

**Starting date:** 2002

**Duration (years):** 3

**Funds allocated for project - total in Czech crowns:** 1800000

#### **Summary of 2004 results**

**Title of the presentation:** Association of coronary atherosclerosis and fatty acid composition of plasma, erythrocyte membrane and serum lipoproteins

**Authors:** Vladimír Bláha (1), Dušan Černohorský (1), Dagmar Solichová (1), Radomír Hyšpler (1), Petr Žďánský (1), Pavel Vyroubal (1), Zdeněk Zadák (1), Faculty Hospital, Charles University, Department of Gerontology and Metabolic Care (1)

Group of aged patients with coronary artery disease (CAD) was studied to analyze the association of coronary atherosclerosis and fatty acid (FA) composition of plasma, erythrocyte membrane and serum lipoproteins. Methods: Forty-six aged patients with CAD, 33 women and 13 men, were examined in three groups based on Crichton Geriatric Rating Scale (CRICHT). Group A were 15 outpatients aged  $93 \pm 3$  years (90-101 years). Group B were 15 control outpatients aged  $83 \pm 5$  years (75-89 years). The patients in Groups A and B were self-sufficient, without any acute major illnesses and free living. Group C were institutionalized patients from nursing facility aged  $93 \pm 3$  years (90-96 years) with CAD and were disabled subjects without any acute major illnesses. Free FA (FFA), saturated FA (SUFA), and polyunsaturated FA (PUFA) in plasma, erythrocyte membrane and serum lipoproteins were assessed by capillary gas chromatography. Results: Groups A, B and C did not differ in plasma total cholesterol, its fractions of VLDL, HDL, LDL, triacylglycerols and FFA. Institutionalized nonagenarians in Group C had higher CRICHT rating ( $23,3 \pm 8,7$  vs  $15,3 \pm 4,2$  and  $13 \pm 2,2$  in Groups A and B,  $p=0,11$ ), increased LDL and HDL palmitic (C16:0) and stearic (C18:0) SUFA ( $p<0.05$ ), and decreased LDL and HDL linoleic PUFA (C18:2n-6) ( $p<0.05$ ). There were significantly increased erythrocyte membrane C18:0, decreased C18:2n-6, and increased C22:6n3 (docosahexaenoic) FA ( $p<0.05$ ) in Group C. The PUFA omega-3 and other omega-6 FA did not differ between groups. Conclusion: In institutionalized nonagenarians with CAD, the higher concentration of SUFAs and decreased PUFAs in LDL, HDL and erythrocyte cell membrane might be parameters related to disability associated with CAD. Supported by grants IGA MZ CR No. NB/6999-3.

**Address for correspondence:** V. Bláha, Department of Gerontology and Metabolic Care, Faculty Hospital, Charles University, Sokolská 581, 50005 Hradec Králové, Czech Republic



**Title of the research project:** Unstable atheromatous plaque: the possibilities to influence the prognosis of clinically important organ atherosclerosis

**Grant Agency:** Ministry of Health

**Project Number:** NR/8062-3/2004

**Principal Researcher:** Vladimír Bláha

**Joint Researchers:** Pavel Vyroubal, Dagmar Solichová, Raomír Hyšpler, Zdeněk Zadák, Milan Bláha, Eduard Havel, Alena Tichá.

**Starting date:** 1.1.2004

**Duration (years):** 3

**Funds allocated for project - total in Czech crowns:** 2000000

**Summary of 2004 results**

**Title of the presentation:** Impact of aggressive lipid lowering with LDL apheresis upon carotid intima-media thickness and endothelial dysfunction

**Authors:** Vladimír Bláha (1), Pavel Vyroubal (1), Dagmar Solichová (1), Radomír Hyšpler (1), Petr Žďánský (1), Zdeněk Zadák (1), Milan Bláha (2), Alena Tichá (1), Eduard Havel (3) Faculty Hospital, Charles Univ., Dept. Gerontol. Metabol. Care (1), Dept. Haematology (2), Dept. Surgery (3)

We aimed to determine whether the effects of long-term low-density lipoprotein apheresis (LA) on atherosclerotic burden as measured by carotid intima-media thickness relate to markers of endothelial dysfunction in patients with familial hypercholesterolemia. Methods: chronic biweekly LDL-apheresis based on immunoabsorption has been used to treat nine patients with familial hypercholesterolemia. Carotid artery intima-media thickness (IMT) was measured yearly during four years. Plasma concentrations of soluble adhesion molecules (sAMs) marking endothelial dysfunction such as E-selectin, P-selectin and monocyte chemoattractant protein (MCP-1) were measured by ELISA (RDS, USA), with the sets: Parameter human sP-selectin, Parameter human sE-selectin, Quantikine human MCP-1. Results: During four years of treatment with LA, atherosclerotic burden as measured by carotid artery intima-media thickness showed progression in 3 patients, and related mainly to increased MCP-1, regression occurred in 2 patients, and any change was in 4 patients. Any of the patients did not suffer from a new atherosclerotic vascular event during the study. Before LDL-apheresis, P-selectin was increased versus control ( $202 \pm 48$  ng/ml,  $p < 0,05$ ). After LDL-apheresis, P-selectin and MCP-1 significantly decreased ( $p < 0,05$ ). The concentrations of all sAMs studied were significantly lower in the plasma leaving than entering the filter. We conclude that in addition to lipid reduction, LDL apheresis significantly improves the development of atherosclerosis, which is related to the plasma concentrations of soluble adhesion molecules. Supported by grants IGA MZ CR No. NR/8062-3/2004.

**Address for correspondence:** V. Bláha, Department of Gerontology and Metabolic Care, Faculty Hospital, Charles University, Sokolská 581, 50005 Hradec Králové, Czech Republic



**Title of the research project:** Study of induction of UCP-2 RNA expression in liver tissue of rats after triiodothyronine administration

**Grant Agency:** Charles University

**Project Number:** 123/2004

**Principal Researcher:** Radka Bolehovská

**Joint Researchers:** Zuzana Červinková, Monika Pospíšilová, Halka Lotková, Pavla Křiváková

**Starting date:** 1.1.2004

**Duration (years):** 2

**Funds allocated for project - total in Czech crowns:** 256000

**Summary of 2004 results**

**Title of the presentation:** Induction of UCP-2 RNA expression after single and repeat administration of triiodothyronine in various tissues

**Authors:** Radka Bolehovská, Zuzana Červinková, Monika Pospíšilová, Halka Lotková, Pavla Křiváková, Fac. Med. Charles Univ., Hr. Králové: Dept. Physiology

Family of uncoupling proteins (UCP) plays important role in regulation of energy metabolism in many tissues, e.g. brown adipose tissue, skeletal muscles. Insufficient information is available about the role of UCP in liver tissue. The aim of our project is:

a) to introduce methods necessary for evaluation of UCP-2 RNA expression (reverse transcription and standard PCR)

b) detailed analysis of UCP-2 RNA expression in various tissues especially in the liver tissue after administration of single and repeat dose of triiodothyronine (200 micrograms/kg of body weight).

During the first year the project continued according to the plan. RNA was isolated using commercial reagents RNA-Blue (Top-Bio, Czech Republic). For isolation tissues gained from male albino Wistar rats (240-250 g) were used. Next step was to introduce PCR for UCP-2, for optimisation of this method it was necessary to select appropriate primer, annealing temperature, concentration of magnesium ions, and optimal type of DNA polymerase. We found the most pronounced induction of UCP-2 RNA 24 hours after triiodothyronine administration in following tissues: kidney, myocardium, skeletal muscles and brain in comparison with control samples. This induction was found also after single administration of triiodothyronine. Surprisingly, we did not find significant change in UCP-2 RNA expression in liver tissue. The reason of this negative result could be time interval in which the induction was measured. Therefore we would like to focus on the dynamics of this expression and also we plan to introduce a quantitative PCR for UCP-2 RNA.

**Address for correspondence:** R. Bolehovská, Department of Physiology, Charles Univ. in Prague, Faculty of Medicine in Hradec Králové, Šimkova 870, 500 38 Hradec Králové, Czech Republic

**Title of the research project:** Innovation of the practical sessions in dental phantom laboratory.

**Grant Agency:** Ministry of Education

**Project Number:** 993/2004

**Principal Researcher:** Daniel Černý

**Joint Researchers:**

**Starting date:** 1.1.2004

**Duration (years):** 1

**Funds allocated for project - total in Czech crowns:** 87000

**Summary of 2004 results**

**Title of the presentation:** Visual demonstration of the work in dental phantom laboratory

**Authors:** Daniel Černý

Charles University in Prague, Medical Faculty in Hradec Kralove, Dental Clinic

The new dental curriculum introduced at the Medical Faculty in Hradec Kralove takes 5 years that have to be used wisely to train those skills important to future dental professionals. Since it is not possible to keep only adding to existing subjects and some topics simply cannot be removed from the curriculum we have to consider greater efficiency of teaching during the time spent at school. Current project has the goal to increase effectiveness during preclinical phantom laboratory work.

The results presented show improved teacher station in the phantom laboratory with appropriate instruments for conservative restorations and equipped with small TV circuit made of one visualiser and two TV monitors. These monitors are to present teachers work to students since proper visual demonstration can sufficiently replace several times longer verbal presentation. Also video presented during lectures cannot be the only solution for this problem as there is a time gap leading to loss of information between lecture and practical session.

Project was supported by the Ministry of Education, No 993/2004.

**Address for correspondence:** Daniel Cerny, Dental Clinic, Faculty Hospital in Hradec Kralove, Sokolska 581, 500 05, Hradec Kralove, Czech Republic

**Title of the research project:** Proteome centre for the study of intracellular parasitism

**Grant Agency:** Ministry of Education

**Project Number:** LN00A03

**Principal Researcher:** Jiří Stulík

**Joint Researchers:** Miroslav Červinka, Jan Krejsek, Emil Rudolf, Hana Andělová, Zdeněk Fiedler, Monika Holická, Martina Loudová, Jakub Novosad, M. Kudlová

**Starting date:** 1.1.2000

**Duration (years):** 2004

**Funds allocated for project - total in Czech crowns:** 2650000

**Summary of 2004 results**

**Title of the presentation:**

**Authors:** M. Červinka (1), J. Krejsek (2), E. Rudolf (1), H. Andělová (1), Z. Fiedler (1), M. Holická (2), J. Novosad (2), M. Loudová (2), M. Kudlová (2), Fac. Med., Charles Univ., Hr. Králové: Dept. of Medical Biology and Genetics (1), Dept. of Clinical Immunology (2)

Our previous data suggest that *Francisella tularensis* is able to manipulate innate immunity cell signalling to escape immune response. The effect of infection by *F. tularensis* on interferon gamma or lipopolysaccharide (LPS) stimulated J774.2 murine macrophage cell line was studied. The changes in the expression of selected surface molecules CD54 (ICAM-1 adhesion molecule), CD86 (B7.2 costimulatory molecule), and CD16/CD32 (receptor for FcIgG molecule) on J774.2 cells were followed by cytoimmunofluorometry.

The significant increase in the expression of only CD16/CD32 is found after LPS stimulation. This effect of LPS stimulation is abrogated by *Francisella tularensis* infection before LPS stimulation. More rapid and enhanced expression of CD16/CD32 molecules is detected on LPS prestimulated J774.2 cells after subsequent *F. tularensis* infection. The expression of both CD54 and CD86 molecules is not influenced by either LPS stimulation or *F. tularensis* infection.

The expression of all CD54, CD86 and CD16/CD32 molecules on J774.2 cells is stimulated by interferon gamma. Slightly diminished expression of these surface molecules is found on J774.2 cells which are infected by *F. tularensis* before interferon gamma stimulation. The expression of both CD86 and CD16/CD32 molecules is highly increased on J774.2 cells which were prestimulated by interferon gamma and then infected by *F. tularensis*.

Time course of infection of *F. tularensis* in J774 and RAW 264.7 macrophages was compared. The killing or survival and multiplication of bacteria within the macrophages was studied. In selected time points acidification of tularemic phagosome was tested using LysoTracker dye.

**Address for correspondence:** M. Červinka, Dept. Med. Biol., Charles University in Prague, Faculty of Medicine in Hradec Králové, Šimkova 870, 500 38 Hradec Králové, Czech Rep.



**Title of the research project:** Serious organ failures, experimental and clinical aspects, possibilities for prevention and therapeutic management

**Grant Agency:** Ministry of Education

**Project Number:** MSM111500001

**Principal Researcher:** Miroslav Červinka

**Joint Researchers:** Jaroslav Cerman, Ivo Dřížhal, Vladimír Geršl, Jiří Horáček, Miroslav Kuba, Yvona Mazurová, Naďa Jirásková, Zbyněk Vobořil, Pavel Živný

**Starting date:** 1. 1.2000

**Duration (years):** 5

**Funds allocated for project - total in Czech crowns:** 3771000

#### **Summary of 2004 results**

**Title of the presentation:** Serious organ failures, experimental and clinical aspects

**Authors:** M. Červinka (1), J. Cerman (2), I. Dřížhal (3), V. Geršl (4), J. Horáček (5), M. Kuba (6), Y. Mazurová (7), N. Jirásková (8), Z. Kaška (9), P. Živný (10) Fac. Med., Charles Univ., Hr. Králové, Depts: Med. Biol. (1), Med. Biochem. (2), Stomatol (3), Pharmacol. (4), Microbiol. (5), Path. Physiol. (6), Histology (7), Ophthalmol. (8), Surgery (9), Clin. Biochem. (10)

In this multidisciplinary project the following topics were studied during 2004: 1) Inducers of apoptosis in the HL-60 cell line using the Western blot analysis of cytosol. Valproate, ligand TRAIL, and ionizing radiation decreased anti-apoptotic protein Mcl-1; and increased activation of caspases 8 and 9 and the release of cytochrome-c to cytoplasm. 2) Combined effect of sodium selenite and camptothecin on cervical carcinoma cells. 3) The evaluation of cardiotropic and cardioprotective effects of new iron chelators from the viewpoint of protein profiling of the myocardium. 4) Comparison of guided tissue regeneration and operation of gingival flap in the treatment of periimplantitis. 5) Optimised set of visual moving stimuli significantly increased sensitivity of visual evoked potentials as proved in Neuroborreliosis and in detection of neurotoxicity of some drugs. 6) The relationship between neurodegenerative process within the striatum and the following neural graft expansion and the influence of both to the cell proliferation in the subependymal layer of the lateral brain ventricles were evaluated. 7) The addition of AdvanTec and NeoSoniX technology significantly reduces the phaco energy. The postoperative results of implantation of the new lenses for small-incision surgery are very good. 8) Infectious complications after organ (kidney) and cell (bone marrow) transplantations. 9) Relationships of biochemical markers to surgical trauma, the serum leptin, albumin, haptoglobin, and cholesterol concentrations demonstrated serious perioperative dynamics, these concentrations are stabilized the 5th postoperative day. 10) Monitoring blood flow and analyte concentrations in an interstitium of different tissues by microdialysis show that the lithium is suitable marker of blood flow.

Project was supported by the Ministry of Education Research Project, No. MSM 111500

**Address for correspondence:** M. Červinka, Dept. Medical Biology and Genetics, Charles University in Prague, Faculty of Medicine in Hradec Králové, Šimkova 870, 500 38 Hradec Králové, Czech Rep.



**Title of the research project:** Hepatology - physiological, pathophysiological and clinical aspects

**Grant Agency:** Ministry of Education

**Project Number:** MSM 11150003

**Principal Researcher:** Zuzana Červinková

**Joint Researchers:** Petr Hůlek, Helena Živná, Jiří Kanta

**Starting date:** 1.1.1999

**Duration (years):** 6

**Funds allocated for project - total in Czech crowns:** 3269000

**Summary of 2004 results**

**Title of the presentation:** Evaluation of acute and chronic liver injury with impact on potential hepatoprotective effect of selected substances in in vivo and in vitro animal experiments, and clinical practice.

**Authors:** Zuzana Červinková (1), Petr Hůlek (2), Helena Živná (1,4), Jiří Kanta (3) Fac. Med. Charles Univ., Hr. Králové: Dept. Physiology (1), 1st Dept. Internal Med. (2), Dept. Med. Biochem. (3), Radio-Isotope Laboratory (4)

The research project continued according to the planed activities. Following main topics were studied during the last year:

- a) Using high-resolution oxygraphy it has been documented that tert-butylhydroperoxide selectively inhibits mitochondrial respiratory-chain enzymes in isolated rat hepatocytes in primoculture-oxidation of NADH-dependent substrates is significantly more sensitive to oxidative stress than oxidation of flavoprotein-dependent ones (Physiol. Res. 54: 0, 2005 - accepted)
- b) Glycerophosphate-dependent hydrogen peroxide production by rat liver mitochondria was studied after enzyme induction by triiodothyronine. Using oxygraphic and luminometric measurement a significant increase of hydrogen peroxide production was found (Physiol. Res. 53: 305-310, 2004).
- c) Hepatoprotective effect of S-adenosylmethionine against thioacetamide injury in vivo has been documented in rat.
- d) Induction of mRNA for UCP2 (uncoupling protein) was found in various tissues after triiodothyronine administration.
- e) Changes in concentration of basal metabolic substrates in the liver, adipose tissue and thymus using microdialysis were studied in rats after ligation of ductus choledochus.
- f) Prospective randomized study focused on the impact of stent cover in patients treated by TIPS (transjugular intrahepatic portosystemic shunt) was performed (Čes. slov. gastroent. hepatol., 58: 172-175, 2004).

**Address for correspondence:** Z. Červinková, Department of Physiology, Charles Univ. in Prague, Faculty of Medicine in Hradec Králové, Šimkova 870, 500 38 Hradec Králové, Czech Republic

**Title of the research project:** Health risk level evaluation of Goeckerman's therapy (UV-B and coal tar) of psoriasis in adults

**Grant Agency:** Ministry of Health

**Project Number:** NR 8154-3/04

**Principal Researcher:** Zdeněk Fiala

**Joint Researchers:** Lenka Borská, Jindra Šmejkalová, Jan Krejsek, Ctirad Andrýs, Květoslava Hamáková

**Starting date:** 1. 1. 2004

**Duration (years):** 3

**Funds allocated for project - total in Czech crowns:** 1204000

**Summary of 2004 results**

**Title of the presentation:** Selected biochemical, immunological and cytogenetic changes after Goeckerman's therapy of psoriasis in adults

**Authors:** Zdeněk Fiala (1), Lenka Borská (2), Jindra Šmejkalová (1), Jan Krejsek (3), Ctirad Andrýs (3), Květoslava Hamáková (4), Doris Vokurková (3), Jan Kremláček (2). Charles Univ. Medical. Faculty Hr. Králové: Dept. of Hygiene and Prev. Med. (1), Dept. of Pathol. Physiol. (2); Charles Univ. Faculty Hospital Hr. Králové: Dept. Clinic. Immunol. Allerg. (3), Dept. Clin. Dermatol. Vener. Dis. (4).

Objective. The observed group consisted of thirty patients with psoriasis, undergoing Goeckerman's therapy. Methods. Urinary levels of 1-hydroxypyrene and 1-, 2-, 3-, 4-hydroxyphenanthrene were analyzed by GC/MS. Blood levels of twenty immunological parameters and levels of chromosomal aberrations (CA) in peripheral lymphocytes were determined by standard methods. The PASI (Psoriasis Area and Severity Index) scores evaluated the objective therapy effect. Results. The ointments contain 3 and 5 % of coal tar and the concentrations of total PAH in coal tar samples varied from 29 to 36 %. The levels of urinary metabolites varied: 1-hydroxypyrene (0.97 – 32.71 µg/g creatinine), 1-hydroxyphenanthrene (0.53 – 2.20 µg/g creatinine), 2-hydroxyphenanthrene (0.35 – 13.88 µg/g creatinine), 3-hydroxyphenanthrene (0.35 – 24.75 µg/g creatinine), 4-hydroxyphenanthrene (0.71 – 1.50 µg/g creatinine). Statistic analysis showed significant differences of CA before and after therapy. The levels of IgM, beta-2-microglobulin, alpha-2-macroglobulin and transferrin decreased significantly after the therapy. The level of PASI scores decreased as much as 89 %. Conclusion. Observed parameters changed depending on the therapy length and extent. Some results indicate that the psoriatic patients, treated by highly effective Goeckerman's therapy could be endangered by increased health risk. Supported by the grant No. NR 8154-3/04 of IGA MH Czech Republic.

**Address for correspondence:** Zdenek Fiala, Department of Hygiene and Preventive Medicine, Charles University, Faculty of Medicine, Simkova 870, 50001 Hradec Kralove, Czech Republic

**Title of the research project:** Cardiovascular, Potentially Cardioprotective and Biotransformational Effects of New Iron Chelating Agents.

**Grant Agency:** Czech Republic

**Project Number:** 305/03/1511

**Principal Researcher:** Vladimír Geršl

**Joint Researchers:** Přemysl Poňka, Eva Kvasničková, Michaela Adamcová, Yvona Mazurová, Jana Kaplanová, Martin Štěřba, Tomáš Šimůnek, Eva Čermáková, Olga Popelová

**Starting date:** 1. 2. 2003

**Duration (years):** 3

**Funds allocated for project - total in Czech crowns:** 3445000

**Summary of 2004 results**

**Title of the presentation:** Study of potential cardioprotective effects of a novel group of aroylhydrazone iron chelators in daunorubicin cardiotoxicity in rabbits.

**Authors:** Martin Štěřba (1), Jana Kaplanová (2), Olga Popelová (1), Michaela Adamcová (3), Yvona Mazurová (4), Tomáš Šimůnek (6), Eva Čermáková (5), Vladimír Geršl (1), Přemysl Poňka (7).

Charles Univ.: Fac. Med., Hr. Králové: Dept. of Pharmacol. (1), Dept of Pediatrics (2), Dept. of Physiol. (3), Dept. of Histol. Embryol. (4), Computer Divis. (5); Fac. Pharm., Hr. Králové: Dept. of Biochem. Sci. (6); McGill Univ., Montreal, Canada: Dept. Physiol. Med. (7).

The study aimed to investigate the effects of a novel group of aroylhydrazone iron chelators (PIH - pyridoxal isonicotinoyl hydrazone and SIH - salicylaldehyde isonicotinoyl hydrazone) from the viewpoint of their potential cardioprotective effects in daunorubicin cardiomyopathy in rabbits in vivo. Animals were pre-treated with chelators 60 min before daunorubicin administration; all substances were administered once weekly for 10 weeks. The results in the groups were compared with the daunorubicin group (3 mg/kg, i.v.) and control group (saline). All the PIH pre-treated animals (25 mg/kg, i.p., n = 9) have survived all daunorubicin applications and the changes were in most functional cardiac (e.g. a not significant decrease in LV EF to 53.1 % and in LV dP/dtmax. to 871 kPa/s) and morphological parameters less pronounced than in the daunorubicin group. Furthermore, promising results were obtained also in pilot studies with another chelator – SIH.HCl (50 mg/kg i.p. or 2.5 mg/kg i.v. pre-treatment before daunorubicin administration).

Supported by Grant GA CR No. 305/03/1511.

**Address for correspondence:** V. Geršl, Dept. of Pharmacology, Charles University in Prague, Faculty of Medicine in Hradec Králové, Šimkova 870, 500 38 Hradec Králové, Czech Rep.

**Title of the research project:** The metabolic changes during plan surgery procedure period

**Grant Agency:** Ministry of Health

**Project Number:** NB/7561-3

**Principal Researcher:** Eduard Havel

**Joint Researchers:** Milan Kaška, Petr Motyčka, Radomír Hyšpler, Dagmar Solichová, Zdeněk Zadák

**Starting date:** 2003

**Duration (years):** 3

**Funds allocated for project - total in Czech crowns:** 425000

**Summary of 2004 results**

**Title of the presentation:**

**Authors:**

Tolerance of short-term perioperative starvation or artificial nutritional support indication depends on surgery plan procedure and nutritional state of patient. Short term nutritional support before surgery procedure improves result of surgery in spite usual nutritional markers are not improved (body weight, muscle strength, plasmatic protein level). The aim of the study is to describe changes of some metabolic markers (plasmatic level of insulin like growth factor I - IGF-I, insulin, non-cholesterol sterols, cholesterol and its subtractions, apolipoproteins A-I and B) during different nutritional perioperative strategy: 1. parenteral nutrition for 3 days before, during and after operation, 2. early gastric support after surgery operation, 3. without nutritional support with short several day prolonged period of starvation. The choice of nutritional mode is independent of the study.

The clinical prospective study of monitoring plasmatic metabolic markers changes (IGF-I, cholesterol, apolipoproteins, insulin) during different nutritional perioperative strategies (parenteral, enteral support and starvation) have been started in 2003. The aim of the study is correction of nutritional support decision during surgical procedure based on new arguments and the second aim is to improve knowledge of intestinal metabolic and endocrine anabolic function. More than fifty patients were investigated. Blood samples collection is continuing. Three different groups are not large enough for statistic analysis. Preliminary results describe large interindividual differences in level of IGF-I, but during the short period the level of IGF-I seems to be stabile in every patients. Rapid decrease of lipid parameters during perioperative period is usual. Enteral feeding enhances lipid level recovery. The retention of feeding tube position after surgery procedure is pure.

**Address for correspondence:** Eduard Havel, Teachin hospital, surgery department, 50005 Hradec Králové, Czech Republic, e-mail:havele@lfhk.cuni.cz

**Title of the research project:** Morphological and functional evaluation of radical resections for rectal cancer

**Grant Agency:** IGA, Ministry of Health, CR      **Project Number:** ND/7657-3

**Principal Researcher:** Pavel Hladík

**Joint Researchers:** Zbyněk Vobořil, Iva Pospíšil, Dimitar Hadži Nikolov, Jaroslav Vižďa, Milan Široký, Leoš Ungermann, Josef Dvořák

**Starting date:** 1.1.2003

**Duration (years):** 3

**Funds allocated for project - total in Czech crowns:** 217000

#### **Summary of 2004 results**

**Title of the presentation:** Radioactivity-guided detection of sentinel node in the treatment of rectal cancer.

**Authors:** Pavel Hladík (1), Jaroslav Vižďa (2), Dimitar Hadži Nikolov (3), Josef Dvořák (4), Zbyněk Vobořil (1)

Charles University Teaching Hosp., Hradec Králové, Czech Rep.: Dept. of Surgery (1), Dept. of Nuclear Medicine (2), Dept. of Pathology (3), Dept. of Oncology (4).

Detection of the sentinel nodes has been performed in various kinds of malign disease. The aim of this study is to evaluate the results of the methodology that is based on the use of radioisotope <sup>99m</sup>Tc for sentinel node detection during the surgical treatment of the rectal cancer.

In 2003 – 2004 38 patients (22 males and 16 females, average age 62.3 and 66.1 years) were examined during the operation of the rectal carcinoma. The Miles abdominoperineal rectum resection was performed in 8 cases, the other patients underwent the rectum resection by the method of total mesorectal excision. On the day of the operation the transanal submucosal insertion of the colloid marked by radioactive <sup>99m</sup>Tc was performed. The scintigraphy followed after 3 hours. After the operation we performed the radiodetection with hand gamma probe of the surgical specimen that marked the areas with higher radioactivity, where the sentinel node were expected. The mesorectum was examined by a histopathologist. All the detected lymph nodes were examined by H&E staining, in case of the negative findings the immunohistochemical examination by cytokeratine was used.

In the group of 38 patients the data gained by scintigraphy and radiodetection were in accord with the ones of histopathologic proof of the sentinel node in 33 cases. It was proof of positive results in 31 cases and of negative results in 2 cases. The sensitivity of the method in this group of patients was 86.6%. Radioactivity-guided detection of sentinel node in radical operation of rectum is a method with quite a high sensitivity. It is used to indicate the nodes that would be examined to detect the presence of possible micrometastases.

The project is supported by the Grant Agency of Ministry of Health, Czech Rep.

#### **Address for correspondence:**

Radioactivity-guided detection of sentinel node in radical operation of rectum is a method with P. Hladík, Dept. of Surgery, Charles Univ. Teaching Hosp. Sokolská 581, Hradec Králové, 500 05, Czech Rep.





**Title of the research project:** The possibilities to affect the negative protein balance in severe illness - the effect of proteasome inhibitors

**Grant Agency:** Czech Republic

**Project Number:** 303/03/1512

**Principal Researcher:** Milan Holeček

**Joint Researchers:** Jana Kadlčíková, Roman Šafránek, Jaroslav Chládek, Tomáš Muthný

**Starting date:** 1. 1. 2003

**Duration (years):** 3

**Funds allocated for project - total in Czech crowns:** 1684000

**Summary of 2004 results**

**Title of the presentation:** Effect of proteasome inhibitor MG 132 on protein metabolism in whole body and isolated skeletal muscle of laboratory rat.

**Authors:** Milan Holeček (1), Jana Kadlčíková (2), Roman Šafránek(1), Tomáš Muthný (2)  
Dept. of Physiology, Fac. Med. (1), Dept. of Pharmacology, Fac. Pharm. (2), Charles Univ, Hr. Králové.

Proteasome inhibitors are novel therapeutic agents which may be used in treatment of cancer and other severe disorders. One of the possible side effects off their administration are disturbances in protein metabolism which may affect outcome of the illness. Two separate studies were performed using Wistar rats. In the first study, proteasome inhibitor MG 132 (Sigma Chemicals, St Louis, MO) diluted in dimethyl sulfoxide (DMS) was administered intraperitoneally in dose 10 mg/kg b.w. Controls consisted from DMS treated animals. Changes in protein and amino acid metabolism were estimated in steady state conditions using continuous infusion of L-[1-14C]leucine two hours later. In the second study, m. soleus (SOL) or m. extensor digitorum longus (EDL) were incubated in medium containing 30 mmol/l MG 132 or without MG 132 (control). Protein synthesis was evaluated using L-[1-14C]leucine. Proteolysis was determined according to the rate of the tyrosine release into the medium during incubation. Mann-Whitney (in vivo study) and paired t-test (in vitro study) were used for statistical analysis. In MG 132 treated animals a significant increase in whole-body protein synthesis and proteolysis were observed. However, in in vitro study, MG 132 significantly decreased both protein synthesis and proteolysis. The study was supported by a grant of GACR No. 303/03/1512.

**Address for correspondence:** M. Holeček, Dept. of Physiology, Charles University in Prague, Faculty of Medicine in Hradec Králové, Šimkova 870, 500 38 Hradec Králové, Czech Republic

**Title of the research project:** The occurrence of malnutrition and deficient states in the patients of higher age admitted to hospital. The influence of their stay in the hospital and the possibilities of nutrition support.

**Grant Agency:** Ministry of Health

**Project Number:** 8159-3

**Principal Researcher:** Dana Hrnčiariková

**Joint Researchers:** Zdeněk Zadák, Radomír Hyšpler, Michal Hrnčiarik

**Starting date:** 1.1.2004

**Duration (years):** 3

**Funds allocated for project - total in Czech crowns:** 879000

**Summary of 2004 results**

**Title of the presentation:** The assessment of the nutrition state of the elderly patients in the course of hospitalization.

**Authors:** Dana Hrnčiariková(1), Zdeněk Zadák(1), Radomír Hyšpler(1), Michal Hrnčiarik(2)

University Hospital in Hradec Králové: Dept. of Gerontology and Metabolic Care (1), Dept. of Pneumology (2)

Nutrition plays an important role in the care of an elderly person, because it significantly influences the whole organism - physical and psychological ability, resistance against infection, better management of stress and also faster healing of wounds. In the old aged and ill people we find more often protein deficit, deficiency of vitamins and trace elements indicating insufficient intake of these elements in food in comparison with younger age groups. In our study we can evaluate the state of nutrition in patients of older age that are hospitalized in the Faculty hospital, the impact of their hospitalization and possible nutritional support, on the change of nutritional parameters and deficiency of the vitamins. In the study we include patients aged 80 and older, which are admitted for hospitalization in the standard ward of the Department of Gerontology and Metabolic Care. The assessment of the nutrition state of the patients is made with emphasis on finding out the nutrition anamnesis (Mini Nutritional Assessment - MNA), measuring of the anthropometrical signs (BMI, the circumference of waist, hips and arm, measuring the thickness of the skin fold, testing with dynamometer etc.), biochemical evaluation (serum concentrations of total protein, albumin, prealbumin, transferrin, lipids, vitamins, the level of creatinine in urine etc.) and evaluation of the state of immune system (leucocytes, neopterin in urine etc.). It seems that hospitalization influences negatively the nutritional parameters of our elderly patients.

Project was supported by the Ministry of Health Grant Agency, No 8159-3.

**Address for correspondence:** Dana Hrnčiariková, Dept. of Gerontology and Metabolic Care, University Hospital in Hradec Králové, Sokolská 581, 500 05 Hradec Králové, Czech Republic

**Title of the research project:** Biochemical markers of inflammation in the exhaled breath condensate of patients with lung disease

**Grant Agency:** Ministry of Health

**Project Number:** NL/7024-3

**Principal Researcher:** Jaroslav Chládek

**Joint Researchers:** Petr Čáp, František Pehal, Jiřina Chládková, Jiřina Martínková, Miroslav Průcha, Irena Krčmová, František Salajka, Lucie Mundlová

**Starting date:** 1.1. 2002

**Duration (years):** 3

**Funds allocated for project - total in Czech crowns:** 3200000

#### **Summary of 2004 results**

**Title of the presentation:** Biochemical markers of inflammation, oxidative and nitrosative stress in the exhaled breath condensate of patients with asthma, allergic rhinitis and chronic obstructive pulmonary disease.

**Authors:** Jaroslav Chladek, Jiřina Martínková (1) Petr Čáp, František Pehal (2), Jiřina Chládková (3), Irena Krčmová (4), František Salajka (5). Faculty of Medicine and Hospital, Hradec Kralove: Dept. of Pharmacology (1), Pediatrics (3), Clinical Immunology and allergology (4), Pulmonary diseases (5). Allergology, Hospital Na Homolce, Prague

Exhaled breath condensate (EBC) is a noninvasively collected fluid from lower airways which contains a variety of inflammatory markers and mediators as well as the products of oxidative and nitrosative stress. The aims of this research project were several-fold: A/ to develop specific analytical techniques for various biomolecules in EBC, B/ to examine the role of pre-analytical factors, and C) to study the influence of asthma, allergic rhinitis and chronic obstructive pulmonary disease on the EBC content of various biomolecules.

Results: For the first time, we were able to demonstrate that gas-chromatography/mass spectrometry can be used to accurately quantify exhaled leukotrienes B<sub>4</sub>, C<sub>4</sub>, D<sub>4</sub> and E<sub>4</sub>. In a largest clinical study published so far, we reported reference limits for exhaled leukotrienes in healthy adults and children and provided the evidence of their increased concentrations in patients with well-controlled asthma: Cap P, Chladek J, Pehal F, et al. Gas chromatography /mass spectrometry analysis of exhaled leukotrienes in asthmatic patients. Thorax. 2004 ;59:465-70 (IF 4.1, 3-times cited). In further clinical studies, the measurement of EBC concentrations of leukotrienes, nitrite/nitrate, nitrotyrosine, nitrosothiols, malondialdehyde, and glutathione have been shown promising in diagnosis, evaluation of disease activity and monitoring of pharmacotherapy of patients with lung disease (Cap P, Pehal F, Chladek J, Maly M: Analysis of exhaled leukotrienes in nonasthmatic adult patients with SAR, Allergy 2005, in print; Chladkova J, Krcmova I, Chladek J, Cap P, et al. Validation of nitrite and nitrate measurement in exhaled breath condensate, Respiration 2005, in print).

**Address for correspondence:** Jaroslav Chládek, Dept. of Pharmacology, Charles University, Faculty of Medicine, Šimkova 870, 500 38 Hradec Králové, chladekj@lfhk.cuni.cz



**Title of the research project:** Evaluation and prevention of long-term adverse effects of psoriasis therapy with low-dose oral methotrexate.

**Grant Agency:** Ministry of Health

**Project Number:** NR/7947-3

**Principal Researcher:** Jaroslav Chládek

**Joint Researchers:** Jiřina Martínková, Jiří Grim, Jaroslava Vaněčková, Marie Šimková

**Starting date:** 1.1. 2004

**Duration (years):** 3

**Funds allocated for project - total in Czech crowns:** 1500000

**Summary of 2004 results**

**Title of the presentation:** MTX pharmacokinetics and therapeutic and adverse effects in the initial phase of psoriasis treatment.

**Authors:** Jaroslav Chladek, Jiřina Martínková (1), Jiří Grim (2), Jaroslava Vaněčková, Marie Šimková (3)

Depts. of Pharmacology (1), Internal Medicine (2), and Dermatology (3), Faculty of Medicine and Faculty Hospital, Hradec Králové

The chief problem of systemic antipsoriatic therapy with low-dose oral methotrexate (MTX) is to attain long-term efficacy with acceptable toxicity. The aim of the project is, first, to analyze the factors influencing the risk of chronic adverse effects (hepatotoxicity, myelotoxicity) of pharmacokinetically-guided therapy with MTX (genetic polymorphism of folate-metabolizing enzymes, folate supplementation, comorbidity, etc.), and second, to evaluate possible early bioindicators of toxicity (folates, homocysteine, serum markers of liver fibrosis and cirrhosis, etc.).

During the first year of the projects, PK-guided therapy with MTX was started in 20 patients. The mean plasma homocysteine levels steadily rose from 10.2 (SD 3.3) at baseline to 13.7 (SD 2.9) micromol/l at week 13 ( $p < 0.005$ , one-way ANOVA for repeated measures) with a trend towards a further increase beyond the 13-week period. PK/PD analysis revealed a highly significant inverse relationship between the PASI score and the steady-state AUC of MTX ( $N=22$ ,  $\rho = -0.86$ ,  $p < 0.0001$ ). This result together with the analysis of combined data from all our studies ( $N=65$ ,  $\rho = -0.82$ ,  $p < 0.0001$ ) confirmed the AUC as a predictor of the therapeutic effect. No significant changes in the results of other laboratory test were found except of a small decrease in median leukocyte count and a small increase in median AST activity. In the second year of the project, a prospective controlled study will be organized with concomitant MTX and folic acid administration.

**Address for correspondence:** Jaroslav Chládek, Dept. of Pharmacology, Charles University, Faculty of Medicine, Šimkova 870, 500 38 Hradec Králové, chladekj@lfhk.cuni.cz

**Title of the research project:** Expression of connective tissue proteins in rat hepatic stellate cells

**Grant Agency:** GAČR

**Project Number:** 305/03/1513

**Principal Researcher:** Jiří Kanta

**Joint Researchers:** Irena Hanovcová, Alena Jiroutová, Martina Čermáková, Lenka Majdiaková, Renata Köhlerová, Jaroslav Cerman

**Starting date:** 1.1.2003

**Duration (years):** 3

**Funds allocated for project - total in Czech crowns:** 1383000

**Summary of 2004 results**

**Title of the presentation:** Expression of cytoskeleton antigens in hepatic stellate cells isolated from cirrhotic rat liver

**Authors:** Alena Jiroutová, Jaroslav Cerman, Jiří Kanta

Fac. Med., Charles Univ., Hradec Králové: Dept. of Medical Biochemistry

The expression of antigens in the stellate cells isolated from normal rat liver was similar to that described previously by others. Vimentin was present in the cells at 2 and 7 days after plating, respectively. The expression of desmin increased with time in cell culture. Alpha-smooth muscle actin could not be detected in the first 2 days after isolation but its expression was pronounced after 7 days. On the other hand, glial fibrillar acidic protein (GFAP) was present in the cells only on day 2 after plating.

Liver cirrhosis was caused by 18 doses of carbon tetrachloride. The toxin was administered to rats intragastrically twice weekly. The concentration of vimentin and desmin in the stellate cells isolated from cirrhotic liver was similar to that in normal cells. Alpha actin was present as early as 2 days after isolation and its expression further increased by cultivation. GFAP was absent in the cells from cirrhotic liver.

The phenotype of normal stellate cells changes to myofibroblastic one when the cells are cultured on plastic. We have found that these changes are even more pronounced in the cells isolated from cirrhotic liver.

**Address for correspondence:** J. Kanta, Dept. of Medical Biochemistry, Charles University in Prague, Faculty of Medicine in Hradec Králové, Šimkova 870, 500 38 Hradec Králové, Czech Republic

**Title of the research project:** The influences of standard preoperative starvation and thirst on general patients' conditions.

**Grant Agency:** Ministry of Health

**Project Number:** NR8037-5/04

**Principal Researcher:** Milan Kaška

**Joint Researchers:** Eduard Havel, Pavel Bareš, Radomír Hyšpler, Miroslav Brtko, Vlasta Tošnerová, Taťána Grosmanová, Zbyňka Petrová, Martin Sluka, Bronislava Schusterová, Zdeněk Grosman

**Starting date:** 1.1.2004

**Duration (years):** 5

**Funds allocated for project - total in Czech crowns:** 731000

#### **Summary of 2004 results**

**Title of the presentation:** Praeoperative starvation and general patients' conditions.

**Authors:** Milan Kaška(1), Eduard Havel (1), Pavel Bareš(2), Radomír Hyšpler(3), Miroslav Brtko(4), Vlasta Tošnerová (5), Taťána Grosmanová (1a), Zbyňka Petrová(2a), Martin Sluka (3a), Bronislava Schusterová(4a), Zdeněk Grosman(5a).

Medical Faculty of UK, Hradec Králové : (1) Dept. of Surgery, (2)Dept. of Anesthesiology, (3) Dept. of Clinical Biochemistry,(4)Dept. of Cardiosurgery, (5) Dept. of Rehabilitation, (a) Teaching Hospital of UP, Olomouc: (1)SCICU, (2) Dept. of Anesthesiology, (3) Dept. of Cardiology, (4) Dept. of Rehabilitation, (5) Dept. of Medical Biophysics.

A surgical operation is a trauma inducing a stress reaction of the whole organism and preoperative preparation is very importance part of surgical treatment. Solutions of higher sugars and electrolytes can mitigate postoperative stress reaction and improve comfort of the patients.

We want to focus on the general conditions of patients during of short preoperative and postoperative periods by using various methods of their preoperative preparation in this clinical trial. The patient are divided in three groups according above mentioned methods of preoperative preparation: a/ standard starvation, b/ parenteral nutrition, c/ peroral nutrition. The trial is focused on patients with diseases of large bowel of various ethiology. Many biochemical markers (including serum concentrations of insulin, CDT, CRP, electrolytes, cholesterol etc.). muscle power, heart functions and subjective comfort of patients are investigated.

The first measured results are collected and after statistical analysis they will be publiced during year 2005.

**Address for correspondence:** Milan Kaška, Teaching Hospital, Dept. of Surgery, 50005, Hradec Králové, Czechia, e-mail: kaskam@lfhk.cuni.cz

**Title of the research project:** Dental Implantology – the multimedia educative presentation

**Grant Agency:** Ministry of Education

**Project Number:** 999/F3/d

**Principal Researcher:** Dana Kopecká

**Joint Researchers:** Antonín Šimůnek

**Starting date:** 1.1.2004

**Duration (years):** 1

**Funds allocated for project - total in Czech crowns:** 120000

**Summary of 2004 results**

**Title of the presentation:** Dental Implantology – the multimedia educative presentation

**Authors:** Dana Kopecká, Antonín Šimůnek

Fac. Med., Charles Univ., Hr. Králové: Dept. of Stomatology

The aim of this project is the production of a multimedia educative presentation which deals with the basic principles of dental implantology. The presentation contains text in the Czech language, eighty clinical photos, fifteen diagrams and figures, two animations and six short videosequences of operations (implantations on the model, sinus lift, bone splitting, bone spreading and flapless operation). The written text is completed with spoken commentary. The content is divided into twelve chapters: history, osseointegration, morphology of implants, indications, contra-indications, therapeutic plan, surgical principles, prosthetic principles, augmentation procedures, complications, recall and trends. Every chapter consists of several subchapters. Students can move forward through the presentation at their own speed.

The presentation has been created for students of the dentistry branch of the Czech medical faculties. It will be distributed on CD-ROMs and through the computer server of the Medical Faculty in Hradec Králové. We consider that this material will improve the undergraduate study of dental implantology. This multimedia presentation completes the information introduced in the first Czech implantological monograph „Dental Implantology“.

Literature: A. Šimůnek et al.: Dental Implantology. Nucleus HK, Hradec Králové 2001.

Project was supported by the Ministry of Education Grant Agency, No. 999/F3/d.

**Address for correspondence:** D. Kopecká, Dept. od Stomatology, Faculty Hospital, 500 05 Hradec Králové, Czech Republic, e-mail: kopecdan@fnhk.cz.



**Title of the research project:** Uterine fibroids and insulin resistance

**Grant Agency:** Ministry of Health

**Project Number:** NR 8057

**Principal Researcher:** Milan Košťál

**Joint Researchers:** Alena Šmahelová, Jana Náteková

**Starting date:** 1.1.2004

**Duration (years):** 2

**Funds allocated for project - total in Czech crowns:** 526000

**Summary of 2004 results**

**Title of the presentation:** Uterine fibroids and insulin resistance

**Authors:** Milan Košťál (1), Alena Šmahelová (2), Jana Náteková (1)  
Dept. of Obstetrics and Gynecology (1), Dept. of Metabolic Care and Gerontology (2)

Obesity and hypertension are known risk factors for uterine fibroids. Together with hyperglycemia and dislipidemia these disorders are components of the insulin resistance syndrome. Relation between obesity and fibroids and hypertension and fibroids led us to hypothesis that insulin resistance might also be a risk factor for uterine fibroids. The project is based on assessment of insulin resistance using insulin test in women with fibroids which are not postmenopausal. It is our aim to find eventual relation between the two entities and establish risk ratios.

So far we examined 28 women with fibroids and 12 healthy controls - we performed vaginal ultrasound to assess the size of fibroids and uteruses, insulin test, lipidogram a hormonal profile in all of the participants. They also filled in Quality of Life Questionnaire for women with fibroids. We intend to continue examining 110 new participants. The results will be statistically processed after we have done at least 70-80 tests.

Project is supported by the Ministry of Health Grant Agency, No. NR 8057

**Address for correspondence:** MUDr. Jana Náteková, Dept. of Obstetrics and Gynecology, Teaching Hospital Hradec Králové, 50003 Hradec Králové, Czech Republic

**Title of the research project:**

Comparison of efficacy of two allergen immunotherapy application forms (sublingual and subcutaneous) in treatment of pollinosis, using clinical and laboratory parameters

**Grant Agency:** Ministry of Health**Project Number:** NI/7470-3**Principal Researcher:** Irena Krčmová**Joint Researchers:** Yvona Hanzálková, Ctirad Andrýs, Doris Vokurková, Marcela Drahošová**Starting date:** 1.1.2003**Duration (years):** 2**Funds allocated for project - total in Czech crowns:** 897000**Summary of 2004 results****Title of the presentation:** see above**Authors:** Irena Krčmová, Yvona Hanzálková, Ctirad Andrýs, Doris Vokurková, Marcela Drahošová

Inst. of Clinical Immunology and Allergy, Faculty Hospital, Charles Univ. Hradec Králové

Allergen immunotherapy (AIT) is the only therapeutic approach in the treatment of IgE mediated allergies which is able to target immunopathogenetic process. Allergen could be administered by subcutaneous injection or sublingually. The aim of this study is the comparison of the influence of two types of AIT. Together 62 patients (31 male, 31 female) with grass pollen allergy were enrolled. Subcutaneous AIT (Phostal) was administered to 21 patients. Sublingual AIT (Staloral) was administered to 18 patients. 23 patients were treated symptomatically. Blood samples were collected before the start of therapy (January, 2003) and after 12 months. The following laboratory parameters are followed: total IgE, spec. IgE and IgG4, IFN gamma, IL-4,5, intracellular production of cytokines is determined, namely production of IL-4, IFN gamma in cellular sub-population of CD4+ after stimulation by mitogens. The results obtained: No significant differences in tested parameters were found between groups before the start of study. There is significant increase of IFN gamma in the group of subcutaneous AIT after 12 month of therapy ( $26.0 \pm 16.4$  pg/ml v.  $42.8 \pm 21.8$  pg/ml,  $p < 0.016$ ). We observed no significant changes in the control group and the group of sublingual AIT. There is significant increase of IL-4 in the group treated by subcutaneous AIT after 12 month of therapy ( $8.1 \pm 2.8$  pg/ml v.  $11.2 \pm 4.9$  pg/ml,  $p < 0.022$ ). The IL-5 demonstrated significant decrease only in the group treated by subcutaneous AIT after 12 month ( $6.7 \pm 3.8$  pg/ml v.  $4.8 \pm 2.1$  pg/ml,  $p < 0.05$ ). There is significantly higher level of allergen specific IgG in patients treated by subcutaneous form of AIT in comparison with patients treated by sublingual form ( $101.2 \pm 82.0$  µg/ml v.  $22.4 \pm 10.6$  µg/ml,  $p = 0.002$ ). The changes of serum levels of IL-4, IFN gamma correlated with intracellular production of these cytokines.

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**Title of the research project:** Comparison of energy metabolism in liver homogenate, isolated mitochondria and isolated and cultivated hepatocytes

**Grant Agency:** Charles University

**Project Number:** 126/2004

**Principal Researcher:** Pavla Křiváková

**Joint Researchers:** Zuzana Červinková, Halka Lotková, Tomáš Roušar, Otto Kučera

**Starting date:** 1. 1. 2004

**Duration (years):** 2

**Funds allocated for project - total in Czech crowns:** 246000

**Summary of 2004 results**

**Title of the presentation:** Comparison of energy metabolism in liver homogenate, isolated mitochondria and isolated hepatocytes

**Authors:** Pavla Křiváková, Zuzana Červinková, Halka Lotková, Tomáš Roušar, Otto Kučera  
Charles Univ. Prague, Fac. Med. Hr. Králové: Dept. Physiology

The aim of this study was to measure energy metabolism using high-resolution respirometry (Oxygraph K2, OROBOROS, Austria) in rat liver homogenate, isolated mitochondria and isolated hepatocytes. Comparison of the changes in energy metabolism could help to evaluate mechanism and prognosis of various toxic liver injuries.

During the first year we tested sensitivity of mitochondrial respiratory complex I and II to oxidative damage induced by model toxic substance - tert-butylhydroperoxide (tBHP).

Malondialdehyde concentration measured as a TBARS served as a marker of lipoperoxidation, mitochondrial membrane potential (MMP) was measured spectrofluorimetrically as a change in accumulation of rhodamine 123.

Our results document that tBHP decreases the activity of respiratory complex I and II. These changes are in proportional relation to the tBHP concentration and the time of incubation.

tBHP also increases lipoperoxidation and decreases MMP.

We found that the respiratory complex I activity is much more sensitive to the peroxidative action of tBHP than the activity of complex II.

We obtained similar results in rat liver homogenate, isolated mitochondria and isolated hepatocytes permeabilized by digitonin. All three models seem to be useful for the study of liver energy metabolism.

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**Title of the research project:** Electrophysiological evaluation of age related changes in visual perception of man

**Grant Agency:** Czech Republic

**Project Number:** 309/02/1134

**Principal Researcher:** Miroslav Kuba

**Joint Researchers:** Jana Langrová (Chlubnová), Zuzana Kubová, Jan Kremláček, František Vít, Jana Szanyi, David Gayer

**Starting date:** 1.1.2002

**Duration (years):** 3

**Funds allocated for project - total in Czech crowns:** 1,038,000.-

#### **Summary of 2004 results**

**Title of the presentation:** Electrophysiological criteria for maturation and ageing processes within the visual pathway

**Authors:** Miroslav Kuba, Jana Langrová, Jan Kremláček, Zuzana Kubová, František Vít  
Dept. of Pathophysiology, Charles University-Faculty of Medicine in Hradec Králové, CZ

Visual evoked potentials (VEPs) were tested in the group of 70 healthy subjects in the age span of 6 – 60 years, using selective activation of the parvo- and magnocellular subsystems of the visual pathway by means of pattern and motion stimuli (for demonstration see <http://www.lfhk.cuni.cz/elf>).

Monocular stimulation of both eyes with 7 various stimuli (repeated at least twice) was performed and VEPs from 6 scalp derivations were recorded. Peak latencies and inter-peak amplitudes (altogether 420 parameters and 58,800 values) were evaluated to describe their age dependent changes and topographical characteristics. This study served for constitution of norms in our extended diagnostic examination of VEPs.

Non-significant changes of pattern-reversal VEPs latencies in the whole age-range can be interpreted as a sign of relatively early maturation of the parvocellular system and its functional endurance toward elderly. The found negative correlation between amplitudes and age of subjects in VEPs of this type, mainly when small (10 min of arc) pattern size was used, is explainable due to “high-voltage” EEG in children and partially due to decreasing visual acuity in older subjects.

On the other hand the motion-onset VEPs displayed dramatic configuration development and shortening of latencies up to about 15 years of age and their significant prolongation from about 50 years of age. This documents so far not well described long maturation of the magnocellular system and simultaneously its much lower functional stability - higher sensitivity to various factors leading to senile changes.

Because of inter-individual (partially age dependent) differences in cortical topography of visual motion processing, multi-channel motion-onset VEPs recordings are necessary (besides Oz at least lateral occipital and parietal derivations).

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**Title of the research project:** Acetylsalicylic acid (ASA) resistance in patients with ischemic heart disease (IHD) and changes of thrombocyte function at non responders to ASA as bioindicators of the treatment strategy and prognosis of these patients

**Grant Agency:** IGA

**Project Number:** NR 8036-3

**Principal Researcher:** Malý Jaroslav

**Joint Researchers:** Pecka Miroslav, Pudil Radek, Gregor Jaroslav, Malý Radovan, Kopecký Otakar

**Starting date:** 2004

**Duration (years):** 3

**Funds allocated for project - total in Czech crowns:** 699000

#### **Summary of 2004 results**

**Title of the presentation:** Acetylsalicylic acid (ASA) resistance in patients with ischemic heart disease (IHD) and changes of thrombocyte function at non responders to ASA

**Authors:** Malý Jaroslav, Pecka Miroslav, Pudil Radek, Gregor Jaroslav, Malý Radovan, Kopecký Otakar

The first aim of the study was to assess the prevalence of ASA resistance in patients with ischemic heart disease (IHD) by the use of two independent methods: Platelet aggregation in platelet rich plasma (PRP) after induction by propyl gallate (CPG) and assessment of platelet function by PFA 100 method.

**Patients:** Patient population were consist of 424 patients treated for IHD on II. Dept of Internal Medicine, Teaching hospital, Hradec Králové. Age, gender, and the type of diagnosis and the effect of the therapy were characterized in this group of the patients.

**Results:** Of the 424 patients studied, by CPG platelet aggregation, 51 [12,1%] were resistant to 100 mg/day aspirin and 32 (7,6%) were resistant to 200mg/day aspirin. The PFA-100 system allows quantitative assessment of platelet function, reporting platelet aggregability and detects no difference between the effects of low and high-dose aspirin on platelet function. We found that 37 patients (15,3%) were aspirin resistant according to the PFA-100.

Aspirin resistance is significantly associated with an increased risk death.

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**Title of the research project:** Pathogenesis, diagnosis and therapy of malignant diseases.

**Grant Agency:** Ministry of Education

**Project Number:** MSM111500002

**Principal Researcher:** Jaroslav Malý

**Joint Researchers:** Emil Rudolf , Miroslav Červinka , Zdeněk Fiedler , Vladimír Geršl(2), Michaela Adamcová , Milan Rešl , Pavel Jandík , Zbyněk Vobořil , Jan Bureš , Kopáčová , Jiří Horáček , Alice Poznarová , Jaroslav Malý , Martin Blažek , Bohuslav Melichar , Pavlína Králíčková , Miroslav Kmoníček , Pavel Žák , Ladislav Jebavý

**Starting date:** 2000

**Duration (years):** 4

**Funds allocated for project - total in Czech crowns:** 5400000

#### **Summary of 2004 results**

**Title of the presentation:** Pathogenesis, diagnosis and therapy of malignant diseases

**Authors:** Jaroslav Malý, Emil Rudolf , Miroslav Červinka , Zdeněk Fiedler , Vladimír Geršl(2), Michaela Adamcová , Milan Rešl , Pavel Jandík , Zbyněk Vobořil , Jan Bureš , Kopáčová , Jiří Horáček , Alice Poznarová , Jaroslav Malý , Martin Blažek , Bohuslav Melichar , Pavlína Králíčková , Miroslav Kmoníček , Pavel Žák , Ladislav Jebavý

The research project continued according to the planned activities. Following main topics were studied during the last year:

In patients with autologous transplantation we found no clinically useful benefit of prophylactic parenteral nutrition. Also, glutamine supplementation was not helpful, and was even connected with apparently worse long-term outcome.

In patients with allogeneic blood stem cell transplantation with reduced intensity of conditioning we established a method for monitoring donor chimerism. We have been using the molecular – genetic method – the polymerase chain reaction. We have been monitoring VNTR sequence (variable number of tandem repeats) and part of Y chromosome.

For the first time transplantation with reduced intensity of conditioning was successfully used in patients with multiple myeloma.

Nephrotoxicity was evaluated in breast cancer patients treated by a dose-dense chemotherapy regimen. As expected, a rise of urinary N-acetyl-□-D-glucosaminidase was observed, but not a reproducible rise of albuminuria. An increase in urinary neopterin after administration of neoadjuvant chemotherapy was observed. Results of regional chemotherapy in patients with liver metastases of gastric carcinoma, breast carcinoma and sarcoma were retrospectively analyzed. We evaluated the results on the field of the carcinoma cell lines, cardiotoxicity and nephrotoxicity of cytostatics, effect of topoisomerase for diagnostic criteria of atypical carcinoids, hemostatic changes during stem cell transplantation and results of non myeloablative transplantation regimen.

Project was supported by the Ministry of Education grant No CEZ -MŠMT 111500002

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**Title of the research project:** Population modelling of wanted and unwanted clinical outcome and surrogate parameters

**Grant Agency:** Ministry of Education

**Project Number:** OC B15.10

**Principal Researcher:** Jiřina Martínková

**Joint Researchers:** Jaroslav Chládek, Jiří Grim, Marie Šimková, Jaroslava Vaněčková, Jan Starý, Ondřej Kalous, Jiří Mayer

**Starting date:** 1.1. 2000

**Duration (years):** 5

**Funds allocated for project - total in Czech crowns:** 2400000

#### **Summary of 2004 results**

**Title of the presentation:** Population modelling of wanted and unwanted clinical outcome and surrogate parameters.

**Authors:** Jiřina Martínková, Jaroslav Chládek (1), Jiří Grim (2), Marie Šimková, Jaroslava Vaněčková (3), Jan Starý (4), Ondřej Kalous, Jiří Mayer (5)

Faculty of Medicine and Hospital, Hradec Kralove: Dept. of Pharmacology (1), Internal Med. (2) and Dermatology (3). Dept. of Hematooncol., Faculty Hospital Motol, Prague (4), 1-rst Dept. of Internal Med. and Hematooncology, Faculty Hospital Brno-Bohunice (5)

The aim of this collaborative research project was to investigate the relationships between wanted and unwanted clinical outcome and surrogate parameters using individual and population modelling of pharmacokinetics (PK) and pharmacodynamics (PD) of drugs used in three therapeutic areas: A/ low-dose oral methotrexate therapy of psoriasis, B/ high-dose methotrexate in acute lymphoblastic leukemia of childhood, and C/ high-dose busulphan in patients with bone marrow transplantation.

Results: A/ a PK/PD relationship between the area under the methotrexate plasma concentrations-time curve and PASI (the Psoriasis Area and Severity Index) has been described and a pharmacokinetic-guided method of dose individualization suggested.

Published in: J Chromatogr B Biomed Sci Appl. 2000;744(2):307-13, Br J Clin Pharmacol. 2002;54(2):147-56, Clin Pharmacokinet. 2003;42(2):139-51, and Basic and Clinical Pharmacology and Toxicology 2005 (in print).

B) a population pharmacokinetic model for high-dose methotrexate has been developed

C) a population pharmacokinetic model for high-dose busulphan has been proposed and compared with the first published model by Sandstrom M et al (Bone Marrow Transplant. 2001;28(7):657-64).

Results of projects B/ and C/ were presented in an invited lecture Martínková J.: Pharmacokinetic Guided Anti-Cancer Treatment, at The 6th Congress of EACPT, Istanbul, Turkey, 2003, and in numerous abstracts. Full-size manuscripts are under preparation.

**Address for correspondence:** Jaroslav Chládek, Dept. of Pharmacology, Charles University, Faculty of Medicine, Šimkova 870, 500 38 Hradec Králové, chladekj@lfhk.cuni.cz





**Title of the research project:** Prediction of metabolic drug-drug interactions based on in vitro experiments.

**Grant Agency:** COST

**Project Number:** B15.30

**Principal Researcher:** Jiřina Martínková

**Joint Researchers:** Stanislav Mičuda, Jolana Cermanová, Jaroslav Chládek, Lucie Mundlová

**Starting date:** 1.1.2000

**Duration (years):** 5

**Funds allocated for project - total in Czech crowns:** 700000

**Summary of 2004 results**

**Title of the presentation:** Prediction of pharmacokinetic drug interactions based on in vitro experiments.

**Authors:** Mičuda S, Mundlová L, Funksa L, Cermanová J, Mokřý J, Osterreicher J, Chládek J, Martínková J.

We investigated the effect of dexamethasone (DEX) on the steady-state kinetics of rhodamine-123 (Rh123), a P-glycoprotein (P-gp) substrate, and the mechanism of this drug-drug interaction. Male Wistar rats were treated with DEX (1 mg /kg per day, p.o.) once a day for 4 days, and the blood, bile and urine concentrations of Rh123 were measured during an i.v. infusion of Rh123 (50 mg/hour) applied 24 hour after the last DEX treatment. The total, biliary and renal clearances of Rh123 and production of urine significantly increased after DEX pretreatment suggesting induction of P-gp expression. Consequent Western blot and immunohistochemical analyses with a monoclonal antibody for P-gp, C-219, revealed that DEX pretreatment increased P-gp level in the liver 4.3-fold, but not in the kidney. In addition, liver expression of another multidrug resistance transporter MRP2 was 1.6-fold higher after dexamethasone. Comparison of the hepatic and renal Rh123 clearances with results of Western blot analyses revealed better correlation of Rh123 pharmacokinetic parameters with MRP2 expression. In conclusion, it was demonstrated that DEX pretreatment affected hepatic exposure to RH123 by increasing the expression of P-gp. Moreover, it seems that MRP2 contributes to transport of Rh123 as well.

This study was performed within the framework of the COST B15.30 project.

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**Title of the research project:** The experimental model of Huntington's disease: The reaction of the subependymal layer of lateral ventricles to neurodegenerative process within the striatum, and to the fetal neural graft.

**Grant Agency:** Ministry of Health

**Project Number:** NF/7594-3

**Principal Researcher:** Yvona Mazurová

**Joint Researchers:** Jan Österreicher, Ivan Látr, Jaroslav Cerman

**Starting date:** 1.1.2003

**Duration (years):** 3

**Funds allocated for project - total in Czech crowns:** 2210000

#### **Summary of 2004 results**

**Title of the presentation:** Increased proliferative activity within the subependymal layer in response to the neurodegenerative process of the striatum in short-term surviving animals.

**Authors:** Mazurová Yvona (1), Österreicher Jan (2), Látr Ivan (3), Cerman Jaroslav (4) Fac. Med., Charles Univ., Hr. Králové: Dept. of Histol. and Embryol. (1), Neurosurg. Clin. (3), Dept. of Med. Biochem. (4); Dept. of Radiobiol., Purkyně Military Acad., Hr. Králové (2)

The unilateral quolinic acid lesion (QA-L) of the striatum was used in rats as a model of neurodegenerative process in Huntington's disease. Formerly we have studied the reaction of the subependymal layer (SEL) in long-term surviving animals (up to 9 months). Now we interested in a short-term response – one week after the QA-L. The sham-lesioned and intact rats were examined as the controls. Immunohistochemical detections of different antibodies, incl. the double-staining and particularly immunofluorescent methods were used on serial coronal paraffin sections.

The neurodegenerative process always increased the cell generation within the SEL, compared with non-lesioned contralateral hemisphere and with intact controls. The sham-lesion also increased the SEL proliferative activity but always markedly less compared with QA-L. Although the enlargement of the SEL was based especially on increased number of GFAP+ astrocytes, not all of those cells expressed also BrdU in their nuclei. High number of NESTIN-positive neural stem cells was typical in the SEL of all lesioned animals and there was also less or more prominent labelling for GFAP of most of these cells in relation to the stage of their differentiation. Interestingly, the NESTIN-GFAP+ astrocytes represented also the typical cell population of reactive gliosis within the damaged striatum. In this location, they were more differentiated (related to the amount NESTIN+ filaments) compared to the SEL. The NCAM-BrdU and NCAM-MAP2 positive neuronal precursor cells, mostly forming the characteristic patches, appeared also in increased number within the SEL, particularly of the lesioned hemisphere.

The work supported by the Ministry of Health of the Czech Republic (NF 7594).

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**Title of the research project:** Modelling and experimental research of thermoinactivation, baroinactivation and growth of selected microorganisms

**Grant Agency:** NA of Agriculture Research

**Project Number:** 1B4404013407

**Principal Researcher:** Pavel Měříčka

**Joint Researchers:** Milan Houška, Vladimír Špelina, Aleš Landfeld, Karel Hoke, Ljuba Schlemmerová, Pavel Čermák

**Starting date:** 1.4.2004

**Duration (years):** 3

**Funds allocated for project - total in Czech crowns:** 1384000

**Summary of 2004 results**

**Title of the presentation:** Application of predictive microbiology in human milk banking

**Authors:** Pavel Měříčka (1), Milan Houška (2), Aleš Landfeld (2), Pavel Čermák (3)

University Hospital Hradec Králové, Tissue Bank (1), Dept. of Clinical Microbiology (3), Food Research Institute Prague (2)

Predictive microbiology is an efficient tool for calculation of the effect of thermoinactivation of human milk (HM) and for estimation of growth of microbes in HM during storage in human milk banks (HMB) (1). In the pilot study (1) the genus *Enterococcus* was identified as the frequent contaminant of HM that can grow even at temperatures near zero. The growth model for this microbe was not known, however. As a result of current investigations the mathematical model of thermoinactivation of *Enterococcus faecium* using the standard collection strain was elaborated for the w.a. 0.99, 0.97 and pH 6.0-7.6 and T 60-65°C. Food micromodel was used for analysis of growth of microbes in the raw and pasteurised milk

stored at temperatures occurring in common refrigerators used in HMB (+2 till +11 °C). In the raw milk the growth of *St. aureus* was analysed, in the pasteurised milk the calculation was made for strains *St. aureus*, *B. cereus* and *E.coli*. It was found that in 48 hour storage of liquid pasteurised HM meeting the quantitative criteria of the Decree of the Ministry of Health of the Czech Republic is scarcely possible even if the practical sterility (less than 1 cfu/ml) is achieved immediately after pasteurisation. The results confirm the advantages of frozen storage of pasteurised human milk used in our practice (1).

References: P. Měříčka et al.: Quantitative assessment of microbiological risk in processing and application of the pasteurised frozen human milk, paper No. ICR0645, IIR/IIF International Congress of Refrigeration, August 2003, Washington, D.C., U.S.A., Proceedings of the ICR2003, ISBN 2-913149-32-4, CD-ROM.

**Address for correspondence:** P. Měříčka, Tissue Bank, University Hospital, Hradec Králové, 500 05 Hradec Králové, Czech Republic



**Title of the research project:** Metabolic drug interactions – importance of cytochrome P450.

**Grant Agency:** FRVŠ

**Project Number:** 1000/F3/d

**Principal Researcher:** Stanislav Mičuda

**Joint Researchers:** Lucie Mundlová, Jolana Cermanová, Jiřina Martínková

**Starting date:** 1.1.2004

**Duration (years):** 1

**Funds allocated for project - total in Czech crowns:** 116000

**Summary of 2004 results**

**Title of the presentation:** Innovation of teaching materials for pharmacology.

**Authors:** Mičuda S, Mundlová L, Cermanová J, Martínková J.

In most therapeutic regimens today, patients take more than one medication at a same time. While some drug combinations do not interact significantly in vivo, other drug combinations can affect the patient's safety and the effectiveness of his or her treatment. For this reason some drug combinations should not be given at all, while other drugs may be used together with caution, possibly requiring adjustments of dosage or time of administration. Alterations in pharmacokinetic profiles commonly occur with concomitant administration of drugs that needs to be metabolized prior to excretion. Cytochrome P450 (CYP) 1A2, 2C9, 2D6, and 3A4 are the major enzymes responsible for oxidative metabolism of drugs. Consequently, a large number of clinically significant drug interactions associated with either CYP inhibition or induction have been documented in literature. Therefore, purpose of this project was to summarize clinically relevant cytochrome P450 drug interactions, their significance, solutions and possibilities for prediction. Collected materials are presented through interactive application freely accessible on internet page of our Department of Pharmacology: <http://www.lfhk.cuni.cz/farmakol/ceska.htm>. Moreover, application contains several case reports of CYP interactions from clinical practice and simple module for calculation of in vivo predictions based on in vitro data.

This study is supported by the grant from the Ministry of Education (FRVS No. 1000/F3d/2004).

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**Title of the research project:** Establishment and exploitation of human hepatocyte culture systems for the in vitro evaluation of drug metabolism

**Grant Agency:** COST

**Project Number:** OC B15.40

**Principal Researcher:** Jaroslav Mokrý

**Joint Researchers:** Dana Čížková, Jana Karbanová, Stanislav Mičuda, Jiřina Martínková, Jaroslav Chládek, Lucie Mundlová, Jolana Cermanová

**Starting date:** 1.1.2002

**Duration (years):** 3

**Funds allocated for project - total in Czech crowns:** 1971000

**Summary of 2004 results**

**Title of the presentation:** Establishment of a system for long-term cultivation of human hepatocyte

**Authors:** Dana Čížková (1), Jaroslav Mokrý (1), Jana Karbanová (1), Stanislav Mičuda (2), Jan Osterreicher (3), Jiřina Martínková (2)

Charles Univ. Prague, Fac. Med. Hradec Králové: Dept. of Histology and Embryology (1), Dept. Pharmacology (2), Purkyně Milit. Med. Acad. Hradec Králové: Dept. Radiobiology (3)

We maintained WRL-68 cells for 2 – 12 weeks in different culture media with the aims to establish a long-term culture of foetal human hepatocytes and to induce their differentiation. The basal cultivation medium consisted of EMEM medium with 10 % foetal calf serum and antibiotics. This medium was enriched with oncostatin M (10 ng/ml), 75 % HepatoZYME-SFM medium and epidermal growth factor (EGF; 20 ng/ml) with dexamethason (10 $\mu$ M) in different experiments. WRL-68 cells were also co-cultivated with embryonic liver cells isolated from mice (17 days of gestation). In all experiments, special culture dishes with a gas-permeable base made of a 25  $\mu$ m thick plastic membrane were used. Membranes covered with several layers of cells were fixed, cut, embedded in paraffin and processed for immunohistochemistry. The basal medium enriched with EGF and dexamethason was evaluated as the best medium for the long-term cultivation of the WRL-68 cell line. Co-cultures of WRL-68 cells and isolated mouse embryonic liver cells were in a very good condition although only the basal medium was used. WRL-68 elements proliferated, formed three-dimensional structures and under suitable cultivation conditions and cell-to-cell interactions, they underwent cellular differentiation. Some morphogenetic processes observed during in vivo hepatogenesis were also noticed in those cultures. 3-D cultures of liver cells represent a more valuable in vitro model than a monolayer and represent a novel human hepatocyte culture system permitting long-term experiments.

This project was supported by the COST grant No. OC B15.40.

**Address for correspondence:** Doc. MUDr. Jaroslav Mokrý, Ph.D., Department of Histology and Embryology, Charles University Medical Faculty, Šimkova 870, 500 38 Hradec Králové



**Title of the research project:** Innovation of topics Blood and Circulatory system

**Grant Agency:** Ministry of Education

**Project Number:** 995/F3a

**Principal Researcher:** Jaroslav Mokrý

**Joint Researchers:** Danuše Šubrtová

**Starting date:** 1. 1. 2004

**Duration (years):** 1

**Funds allocated for project - total in Czech crowns:** 165000

**Summary of 2004 results**

**Title of the presentation:** Circulatory system and Blood: Innovation of lectures and laboratory classes from histology

**Authors:** Jaroslav Mokrý, Danuše Šubrtová

Fac. Med., Charles Univ., Hr. Králové: Dept. of Histology and Embryology

Lectures and programmes for laboratory classes covering the themes of "Circulatory system" and "Blood" were supplemented with new pieces of knowledge, colored versions of 3-D reconstructions, digitalized images of the heart and blood vessels and prepared as computer presentations. New histological sections of human and mouse heart, aorta, large veins, nipple, vagina, lung, spleen, and spinal cord were cut and processed for routine staining and peroxidase immunohistochemistry. The latter detections were focused on endothelial markers (CD31, CD34, vimentin, von Willebrand factor, P-selectin, V-CAM, nestin), basal membranes (collagen IV, laminin, entactin), muscular markers (desmin, SMA) and S-100 protein, marker of visceral innervation. Immunoreactive structures were photographed and used to prepare the database of digitalized images as well as lectures and laboratory classes. Immunostained sections were inserted in sets (boxes) of slides used by teachers. Lectures, programmes of laboratory classes and interactive images are available at web sites:

<http://www.lfhk.cuni.cz/histologie/>.

**Address for correspondence:** Doc. MUDr. Jaroslav Mokrý, Ph.D., Department of Histology and Embryology, Charles University Medical Faculty, Šimkova 870, 500 38 Hradec Králové

**Title of the research project:** Factors influencing the extent of colonization of recipient's tissues by stem cells.

**Grant Agency:** Czech Republic

**Project Number:** 304/03/1515

**Principal Researcher:** Jaroslav Mokřý

**Joint Researchers:** Stanislav Filip, Jana Karbanová, Dana Čížková

**Starting date:** 1.1.2003

**Duration (years):** 3

**Funds allocated for project - total in Czech crowns:** 2321000

**Summary of 2004 results**

**Title of the presentation:** Immunohistochemical analysis of clone-derived neural stem cells in vitro and in vivo following neural grafting

**Authors:** Jana Karbanová (1), Jaroslav Mokřý (1), Stanislav Filip (1, 2)

Fac. Med., Charles Univ. Hr. Králové: Dept. of Histology and Embryology (1), Dept. of Oncology and Radiotherapy (2)

Neural stem cells (NSCs) are cells with self-renewal potential giving rise to neurons and glia. When cultured in vitro single NSCs proliferate and form rounded cell clusters called neurospheres. Nevertheless differences can be found in their size and morphology. The aim of this work was to evaluate phenotype of neural stem cells derived from single NSCs and examine their differentiation potential immunohistochemically after transplantation into the mouse brains. Neural stem cells were isolated from foetal mouse forebrains and cultured in serum-free medium supplemented with basic fibroblast and epidermal growth factors. Using the clonal analysis 4 single NSCs-clones were acquired. However only the one NSC-clone forming large rounded-shape neurospheres survived long term cultivation. These neurospheres expressed weak nestin throughout the neurospheres especially in surface layers. Superficial cells were also found to be A2B5+ and weakly NG2+ but the GFAP immunoreactivity was not detected in the whole neurosphere. This is the difference from the wild-type neurosphere that revealed GFAP in the central parts and intense NG2 positivity in the cells on the periphery as well as stronger nestin and A2B5 positivity in the entire neurosphere. Following transplantation clone-derived NSCs that resided in the striatum were found to differentiate mainly to the GFAP+ astrocyte. Cells that migrated along the corpus callosum were detected as NeuN and Pan NF+ neurons. Sporadic cells were identified as NG2+ oligodendrocyte precursors. This study demonstrates that NSCs clone keeps self-renewal and full differentiation potential and proves the heterogeneity of wild-type NSCs population.

Project was supported by the Grant Agency of the Czech Republic, No. 304/03/1515.

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**Title of the research project:** Therapy of demyelinating disorders of the CNS using neural stem cells

**Grant Agency:** Ministry of Health

**Project Number:** NR7969-3/04

**Principal Researcher:** Jaroslav Mokrý

**Joint Researchers:** Jana Karbanová, Dana Čížková

**Starting date:** 1. 1. 2004

**Duration (years):** 3

**Funds allocated for project - total in Czech crowns:** 1650000

**Summary of 2004 results**

**Title of the presentation:** Generation of oligodendrocytes from neural stem cells

**Authors:** Jaroslav Mokrý, Jana Karbanová, Dana Čížková, Dana Šubrtová

Fac. Med., Charles Univ., Hr. Králové: Dept. of Histology and Embryology

Neural stem cells are multipotent brain tissue-specific stem cells that generate neuronal and glial cells. We isolated neural stem cells from brains of foetal mice using the neurosphere assay, propagated them in vitro via passaging and examined their potential to generate specific CNS cell types. Suspension of foetal neural cells was exposed to mitogenic epidermal and basic fibroblast growth factor in uncoated dishes in chemically-defined medium. Differentiation potential of cultured stem cells was evaluated in vitro and in vivo. Phenotypes of cells arising in differentiation assay were characterized on the basis of their antigenic profile as beta-III tubulin+ neuronal, GFAP+ astroglial and O4+ oligodendroglial cells.

Transplants derived from neural grafting of solid neurospheres contained beta-III tubulin+, synaptophysin+ neuronal cells, GFAP+ astroglial cells and NG2+ oligodendroglial cells. Our data confirm the multipotency of neural stem cells cultured in the neurosphere assay as well as their spontaneous capacity to generate oligodendroglial cells in vitro and in vivo.

**Address for correspondence:** Doc. MUDr. Jaroslav Mokrý, Ph.D., Department of Histology and Embryology, Charles University Medical Faculty, Šimkova 870, 500 38 Hradec Králové

**Title of the research project:** Multimedial teaching of dentistry supported by intraoral camera

**Grant Agency:** Ministry of Education

**Project Number:** 1767/2004

**Principal Researcher:** Štefan Nátek

**Joint Researchers:** Věra Bartáková

**Starting date:** 1.1.2004

**Duration (years):** 1

**Funds allocated for project - total in Czech crowns:** 105000

**Summary of 2004 results**

**Title of the presentation:** Multimedial teaching of dentistry supported by intraoral camera

**Authors:** Štefan Nátek, Věra Bartáková

Faculty of Medicine, Charles University, Hradec Králové, Department of Dentistry

The pre-clinical teaching of dentistry is based on theoretical lectures followed by practicing procedures on models, later on patients in real situations. This teaching method allows us to present a limited amount of procedures, usually in ideal situations. The students still have difficulties with understanding some of problems taught in our curriculum. These include complex common diagnostic and therapeutic procedures as well as very simple, but rare ones. Some diseases, their clinical picture and progress, may present an insuperable obstacle for many students. Ethical, hygienic and time aspects of diagnostic and therapeutic methods performed by students must also be considered.

The aim of this project is to improve practical skills of students of dentistry by application of audiovisual technique. We acquired intraoral camera, AV transducer + software, tools for recording and transmission of data (flash discs, external DVD movie writer, databank, DVD and CD mediums) from funds allocated for our project.

In the first instance, static and dynamic pictures of most frequently performed procedures in oral surgery (i.e. simple extraction of teeth, transalveolar extraction of teeth, intraoral incision, excision of benign tumor) were recorded. Processed recordings were used in practical lessons in the 3rd-5th year of our curriculum and in oral surgery lectures in the 3rd year.

Project was supported by the Ministry of Education, No 1767/2004

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**Title of the research project:** Galanthamine interaction with membrane transport modulators

**Grant Agency:** Internal Grant Agency

**Project Number:** NR 7935-3

**Principal Researcher:** Palička Vladimír

**Joint Researchers:** Květina J., Bajgar J., Živný P., Maláková J., Hrubá P., Svoboda Z., Herink J., Ševelová L.

1) Institute of Clinical Biochemistry and Diagnostics, University Hospital, Hradec Králové

2) Inst. Experimental Biopharmaceutics, Joint Research Centre of PRO.MED.CS Praha a.s. and Academy of Sciences of the Czech Republic, Heyrovského 1207, Hradec Králové

3) Department of Toxicology, Purkyně Military Medical Academy, Hradec Králové, Czech Republic

**Starting date:** 1.1.2004

**Duration (years):** 3

**Funds allocated for project - total in Czech crowns:** 2523000

#### **Summary of 2004 results**

**Title of the presentation:** Comparison of Central and Peripheral Effects of Galanthamine in Rats

**Authors:** Palička V., Svoboda Z., Květina J., Herink J., Bajgar J., Živný P.

Galanthamine (GAL) is a selective, competitive and reversible acetylcholinesterase inhibitor, which increases the activity of the cholinergic system and hence gives rise to an improvement of cognitive functions in patients suffering from dementia of Alzheimer type. The goal of this work was a) comparison of anticholinesterase activity of GAL in the CNS and other tissues, b) selection of suitable dose of GAL for subsequent experiments directed towards modulating its CNS targeting. Thus, GAL was applied intramuscularly to four groups of experimental animals in single doses of 2.5 mg/kg (twice the highest therapeutic dose for humans), 5 and 10 mg/kg. Cholinesterase activity was monitored within 30 minutes following GAL administration in those parts of the brain, which possess a different activity of the cholinergic system (in basal ganglia, septum, frontal cortex and hippocampus) and also in the plasma, liver and hypophysis. The activity of butyrylcholinesterase (EC 3.1.1.8) was evaluated in the plasma and the liver, and that of acetylcholinesterase (EC 3.1.1.7) was evaluated in the hypophysis and brain parts. As regards the most significant results, the highest degree of cholinesterase dose-dependent inhibition was observed in the hypophysis, liver and plasma, while that in the CNS was lower and became apparent in the frontal cortex and hippocampus only after the application of the dose of 10 mg/kg. A relative sensitivity of the frontal cortex was observed in case of other substances, eg. 7-methoxytacrine and various organophosphates, as well. In summary, the dose of 10 mg/kg appears the most effective as well as suitable for future experiments.

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**Title of the research project:** Multimedial teaching files for pediatrics

**Grant Agency:** Ministry of Education

**Project Number:** 1768/F3/d

**Principal Researcher:** Doc. MUDr. Eva Pařízková, CSc.

**Joint Researchers:** MUDr. Pavel Rozsival

**Starting date:** 2004

**Duration (years):** 1

**Funds allocated for project - total in Czech crowns:** 96000

**Summary of 2004 results**

**Title of the presentation:** Multimedial teaching files for pediatrics

**Authors:** P. Rozsival, E. Pařízková

With the support of Ministry of Education a new computer together with a scanner, printer and software (Adobe Acrobat) was bought. With this equipment we were able to digitalize all teaching files for pediatric curriculum, microlectures are in progress. Teaching files in various formats (web page - .html, Power Point presentation - .ppt and on-line presentation - .mhtml, text files - .rtf and portable data format - .pdf) were made available online on web pages of Department of Pediatrics, so that students have the possibility to download them in most convenient format. Interesting cases, reviews, tests etc. will be added as possible.  
<http://www.lfhk.cuni.cz/Karolinka/Department/default.asp?tsk=dep&lng=cz&i=500>

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**Title of the research project:** Surface activation leukocyte markers in cord blood of neonates at risk for early infection

**Grant Agency:** Ministry of Health

**Project Number:** 7533-3

**Principal Researcher:** Doc. MUDr. Eva Pařízková, CSc.

**Joint Researchers:** MUDr. Pavel Rozsival, PharmDr. Doris Vokurková, MUDr. Eva Šimáková, RNDr. Ctirad Andrys, Ph.D., MUDr. Božena Buriánková

**Starting date:** 2003

**Duration (years):** 3

**Funds allocated for project - total in Czech crowns:** 850000

#### **Summary of 2004 results**

**Title of the presentation:** Surface activation leukocyte markers in cord blood of neonates at risk for early infection - preliminary results

**Authors:** P. Rozsival, E. Pařízková, D. Vokurková

**Aim:** To assess surface leukocyte markers in newborns with or without early infection risk.  
**Methods:** Flow-cytometric analysis of lymphocyte, neutrophil and NK-cell markers in cord blood, using monoclonal antibodies.

**Infectious risks:** fetus – prematurity, hypotrophy, hypertrophy, clinical signs of infection after birth, mother – premature rupture of membranes, GBS colonization positive or unknown, febrile delivery.

**Statistics:** Total samples: 125, assessed 92. Control group (no infectious risk, no=33, mean gestational age 39,6 weeks) and Risk group (no=59, mean gestational age 37,2 weeks). MS Excel, NCSS, parametric and non-parametric tests.

**Assessed markers:** CD69, CD25 on CD3+ cells, CD23, CD69 on CD19+ cells, CD38 on CD8+, HLA-DR, CD16, CD64 on CD14+, CD11b on CD16+. CD11b, CD16, CD64 and HLA-DR were compared using absolute counts and mean fluorescence intensity (MFI). CD45RA and CD45RO numbers compared.

**Results (values: mean, (std. dev., 95% LCL of mean, 95% UCL of mean)):**

In newborns at risk, CD14/16 expression was significantly higher: 10.16, (9.38, 7.71, 12.60) vs. 6.14, (3.09, 5.04, 7.23) and CD3/25 expression was significantly lower in risk newborns: 5.29, (2.80, 4.56, 6.02) vs. 6.77, (2.12, 6.00, 7.53).

**Discussion:** Results are preliminary - stratification by unique risks is lacking as well as comparison with regard to outcome (infection vs. infection-free). Consistent with literature, CD16 monocyte expression was higher in risk group. Explanation for lower CD25 expression on T-lymphocytes is lacking - CD25 is an early activation marker.

**Conclusion:** CD16 expression on monocytes is promising in screening for newborns at risk for early infection.

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**Title of the research project:** Intensity- modulated radiotherapy in the reduction of toxicity of anticancer treatment.

**Grant Agency:** Ministry of Health

**Project Number:** NR 8061-3/20

**Principal Researcher:** Jiří Petera

**Joint Researchers:** Karel Odrážka, Milan Vošmik, Milan Zouhar

**Starting date:** 1.1.2004

**Duration (years):** 3

**Funds allocated for project - total in Czech crowns:** 1505000

#### **Summary of 2004 results**

**Title of the presentation:** Intensity - modulated radiotherapy techniques in various clinical situations.

**Authors:** Jiri Petera, Karel Odrážka, Milan Vošmik, Milan Zouhar

Dep. of Oncology and Radiotherapy, University Hospital Hradec Králové

Intensity modulated radiotherapy (IMRT) is a new technique of conformal radiotherapy. IMRT optimally assigns nonuniform intensities (i.e. weights) to tiny subdivisions of beams, which have been called rays or "beamlets". The ability to optimally manipulate the intensities of individual rays within each beam permits greatly increased control over the radiation fluence, enabling custom design of optimum dose distribution. These improved dose distributions potentially may lead to improved tumor control and reduced normal tissue toxicity.

The application, process, and dose distributions of IMRT are significantly different from those of conventional radiotherapy. The traditional methods of specification of treatment, evaluation of treatment plans and reporting of results are limited and new methods need to be introduced.

One hundred fifty patients were treated with IMRT technique at our institution till January 2005. The diagnosis was prostate cancer in 60% of cases, oropharyngeal and nasopharyngeal cancer in 15% and other (low grade gliomas, skull base meningiomas, thyroid cancer, retroperitoneal sarcomas, biliary duct tumors) in 25% of cases.

In the prostate cancer the research was concentrated on development of the standard IMRT technique (class solution), particularly on the definition of rectal dose constraints.

Comparison of IMRT and conventional conformal plans demonstrated substantial reduction of the risk of rectal complications. In the head and neck tumors the technique of integrated IMRT boost and acceleration of the radiotherapy course were tested with promising local tumor control and low acute toxicity. The IMRT for skull base meningiomas resulted in excellent local control with optical nerves and chiasma sparing. Longer follow up is needed to evaluate mature results.



***Address for correspondence:*** Jiri Petera, Dep. of Oncology and Radiotherapy, University Hospital, Hradec Králové

**Title of the research project:** Monitoring quality of care in patients with out-of-hospital circulatory arrest in the East Bohemian region

**Grant Agency:** Ministry of Health

**Project Number:** NO/7254-3

**Principal Researcher:** Miloslav Pleskot

**Joint Researchers:** Jaroslav Kajzr, Zdeněk Tušl, Petr Pařízek, Miroslav Měšťan, Miloslav Tauchman, Jakub Střítecký1, Jiří Kvasnička, Vladimír Černý

**Starting date:** 1.1.2002

**Duration (years):** 3

**Funds allocated for project - total in Czech crowns:** 2030000

#### **Summary of 2004 results**

**Title of the presentation:** Cardiac arrest in the East Bohemian Region: Assessment of out-of-hospital patient care

**Authors:** Miloslav Pleskot(1), Jaroslav Kajzr(1), Zdeněk Tušl(1), Petr Pařízek(1), Miroslav Měšťan(1), Miloslav Tauchman(1), Jakub Střítecký(1), Jiří Kvasnička(1), Anush Babu(1), Vladimír Černý(2), Eva Čermáková(3)

Charles Univ. Prague, Fac. Med. and Univ. Hospital Hr. Králové: Depts Ist Intern. Med.(1), A/E Clinic(2), Med. Biophys.(3)

Introduction: Long-term results of care in patients with out-of-hospital cardiac arrest (CA) are mainly dependent on the quality and organisation of pre-hospital care. Aim: Describe and assess certain indicators of care in patients with out-of-hospital CA in the East Bohemian region. The authors mainly scrutinised the number of patients that were hospitalised and those that were discharged home. Patients and methods: With the aid of a questionnaire supplied to 24 rescue centres in the East Bohemian region over the period from 1.4.2002 to 31.8. 2004, a group of 718 patients (511 men, 207 women) aged 16 to 97 years ( $67 \pm 13$  years) with out-of-hospital CA were included. Results: Most often CA had been announced between 8 and 9 a.m. at home in the month of December. A total of 560 patients (78%) were given professional and 216 (30.1%) layman cardiopulmonary resuscitation (CPR). Most frequently the pre-hospital ECG showed asystoly in 412 cases (57.4%) and in 232 cases (32.3%) ventricular fibrillation. From whole group 159 patients (22.2%) were admitted to hospital as opposed to 498 (69.4%) dying on the spot and 61 patients (8.5%) during transport to the hospital. A further 103 patients (14.4%) died while in hospital. Subsequently only 39 patients (5.4%) were discharged home and 17 patients (2.4%) were transferred to other hospitals. From the 241 autopsied patients a main diagnosis of ischemic heart disease was seen in 204 cases (84.7%) and acute myocardial infarction in 69 cases (28.6%). Conclusion: The results of this project indicate a high lethality in patients with out-of-hospital CA. Only 5.4% of all cases were discharged home. The great number of asystoly on the initial ECG may influence the initiation of professional CPR. Supp. by IGA MZČR NO/7254-3

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**Title of the research project:** Setting the team cooperation principles for the diagnostic and therapeutic management of spinal metastases. Determination of eligibility criteria in patients appropriate for the radical surgery.

**Grant Agency:** Ministry of Health

**Project Number:** 7953-3/2004

**Principal Researcher:** Svatopluk Řehák

**Joint Researchers:** Jiří Náhlovský, Václav Málek, Kurt Kaltofen, Tomáš Česák, Karel Odrážka, Bohuslav Melichar, Vladimír Maisnar, Pavel Ryška, Antoním Krajina

**Starting date:** 1.1.2004

**Duration (years):** 3

**Funds allocated for project - total in Czech crowns:** 994000

#### **Summary of 2004 results**

**Title of the presentation:** Problems of late diagnostics of metastatic spine affections

**Authors:** Svatopluk Řehák(1), Jiří Náhlovský(1), Václav Málek(1), Kurt Kaltofen(1), Tomáš Česák(1), Karel Odrážka(2), Bohuslav Melichar(2), Pavel Ryška(3)

Dept. of Neurosurgery, Faculty Hospital, Hr. Králové(1), Dept. of Oncology, Faculty Hospital, Hr. Králové(2), Dept. of Radiology, Faculty Hospital, Hr. Králové(3)

Present day advancement of the spinal surgery signifies better control-ability of the majority of metastatic spine affections. However, their earlier and successful treatment remains still limited by delayed establishing the correct diagnosis. As an initial metastatic spine affections symptom, local back pain has been reported to occur in 81% of patients and precede the metastatic spine affections diagnosis establishment for 11 weeks on the average. It is known that the development of neurological deficit directly depends on the degree of spinal compression. During the establishment of metastatic spine affections diagnosis, 70 % of respective patients manifested the expressed neurological symptoms that were developed in 15 days on the average. Ability to walk at the beginning of treatment is the most important prognostic factor in patients with the spine metastatic involvement. In the group analysed by the authors, 55% of patients with the neurological deficit were bedridden as in able to walk for 5 days on the average at the time of establishing the diagnosis. This analysis pointed on that the metastatic spine affections graphic diagnosis determination was often performed too late, in spite of several days-lasting history of markedly expressed symptoms of the spinal compression. Specifically, the MRI method is considered a method of choice in identifying the metastatic spine affections cases. This is the only way of how to achieve satisfactory results and prevent from the development of any irreversible neurological changes. In cases of a severe preoperative neurological deficit, even the surgical release of spinal cord may often fail to improve substantially the limbs' motility disorder.

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**Title of the research project:** Effect of growth hormone and glutamine on protein metabolism in isolated skeletal muscle

**Grant Agency:** Ministry of Health

**Project Number:** NB/7611-3/03

**Principal Researcher:** Roman Šafránek

**Joint Researchers:** Milan Holeček, Jaroslav Chládek, Jana Tisančinová, Tomáš Mutný

**Starting date:** 1.1.2003

**Duration (years):** 3

**Funds allocated for project - total in Czech crowns:** 315000

**Summary of 2004 results**

**Title of the presentation:** The effect of sepsis and growth hormone and alanyl-glutamine treatment on protein metabolism in skeletal muscle of the rat

**Authors:** Roman Šafránek (1), Milan Holeček (1), Jana Tisančinová (2), Tomáš Mutný (2)

The aim of the present study was to examine the effects of GH/alanyl-glutamine (Ala-Gln) administration on protein synthesis, protein breakdown and amino acid oxidation and plasma amino acids concentrations of septic rats.

Female Wistar rats were divided into four groups – sham operated (n=12), septic (n=9), septic with GH (1.5 IU/50g/24h) (n=13), and septic with GH and Ala-Gln (180 mg glutamine/50g/24h) (n=16). Sepsis was induced by cecal ligation and puncture. After 18 h of sepsis and drug treatment extensor digitorum longus muscles were dissected. Protein synthesis and leucine oxidation were measured during incubation of muscles with [1-14C]-leucine. One-way ANOVA, \*P<0.05.

CLP resulted in severe sepsis with hemodilution and disseminative intravascular coagulation. In sepsis, plasma levels of aspartate, histidine, phenylalanine and taurine increased, levels of glycine, proline, methionine, lysine, asparagine, serine, and arginine decreased, while there was no significant change in total amino acid concentration. Ala-Gln increased plasma concentrations of alanine and glutamine. In muscles from septic rats, protein synthesis was decreased significantly by 32%, leucine oxidation was increased by 97%, and there were no changes in protein breakdown. GH treatment of septic animals had no effect on measured parameters. Addition of glutamine decreased oxidation of leucine in sepsis to 73% without effect on protein synthesis and protein breakdown.

Cecal ligation and puncture model in rat is a protein wasting condition with resistance to GH. Decreased leucine oxidation by Ala-Gln treatment suggests its favorable effects on branched-chain amino acid and protein metabolism. Sepsis has considerable effect on plasma levels of most amino acids without changing total amino acids concentration.

Supported by a grant NB7611-3/2003 of the IGA MH of the Czech Republic.

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**Title of the research project:** Determination of LPA level in ovarian cancer patients

**Grant Agency:** Ministry of Health

**Project Number:** 7666-3

**Principal Researcher:** Iva Sedláková

**Joint Researchers:** Jindřich Tošner, Jaroslava Vávrová

**Starting date:** 1.1.2003

**Duration (years):** 3

**Funds allocated for project - total in Czech crowns:** 535000

**Summary of 2004 results**

**Title of the presentation:** Determination of LPA level in ovarian cancer patients

**Authors:** Iva Sedláková (1), Jindřich Tošner (1), Jaroslava Vávrová (2)

Fac.Med., Charles Univ., Hr. Králové: Dept. of Gynecology and Obstetrics (1), Dept. of Clin. Biochemistry (2)

Lysophosphatidic acid (LPA, 1-acyl-2-lyso-sn-glycero-3-phosphate) has been shown to stimulate proliferation of ovarian cancer cells. A higher plasma level of LPA in patients with ovarian cancer than those in healthy women was reported. LPA has multiple effects on ovarian cancer cells. The methodics for the LPA level determination with its specifications by capillary electrophoresis using indirect ultraviolet detection has been implemented. Since beginning of this project venous blood samples from 123 patients (42 patients with ovarian cancer, 81 patients without ovarian cancer) have been obtained. Patients with ovarian cancer (OC) had significantly higher plasma LPA level compared with the healthy control group (H) in this project. LPA assesment by capillary electrophoresis using ultraviolet detection allows to determinate single types of lysophosphatidic acid in biological material. There are LPA (M) 1-myristoyl-2-hydroxy-sn-glycerophosphatidic acid (OC med 4,95  $\mu\text{mol/l}$ , range 0,10 - 10,68  $\mu\text{mol/l}$ , H med 0,08  $\mu\text{mol/l}$ , range 0,03-7,03  $\mu\text{mol/l}$ ,  $p < 0,005$ ), LPA (P) 1- palmitoyl-2-hydroxy-sn-glycerophosphatidic acid (OC med 4,42  $\mu\text{mol/l}$ , range 0,40 - 19,03  $\mu\text{mol/l}$ , H med 0,84  $\mu\text{mol/l}$ , range 0,43 - 16,87  $\mu\text{mol/l}$ ,  $p = 0,005$ ), LPA (S) 1-stearoyl-2-hydroxy-sn-glycerophosphatidic acid (OC med 5,92  $\mu\text{mol/l}$ , range 0,55 - 8,56  $\mu\text{mol/l}$ , H med 0,62  $\mu\text{mol/l}$ , range 0,35 - 6,13  $\mu\text{mol/l}$ ,  $p = 0,025$ ) and LPA (O) 1-oleoyl-2-hydroxy-sn-glycerophosphatidic acid (OC med 4,52  $\mu\text{mol/l}$ , range 0,41 - 11,00  $\mu\text{mol/l}$ , H med 0,08  $\mu\text{mol/l}$ , range 0 - 7,63  $\mu\text{mol/l}$ ,  $p < 0,005$ ). Our preliminary results suggest, that plasma LPA level may represent a potential biomarker for ovarian cancer, further results are needed.

Project is supported by the Ministry of Health Grant Agency, No 7666-3

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**Title of the research project:** Sinus lift in dental implantology referring to osseointegrated implant parameters and type of augmentation materials

**Grant Agency:** Ministry of Health

**Project Number:** 7711-3

**Principal Researcher:** Antonín Šimůnek

**Joint Researchers:** Dana Kopecká, Aleš Kohout

**Starting date:** January 1, 2003

**Duration (years):** 3

**Funds allocated for project - total in Czech crowns:** 1593000

**Summary of 2004 results**

**Title of the presentation:** Sinus lift in dental implantology referring to osseointegrated implant parameters and type of augmentation materials

**Authors:** Antonín Šimůnek (1), Dana Kopecká (1), Aleš Kohout (2)

(1) Department of Stomatology, Faculty of Medicine, Charles University, Hradec Králové

(2) Fingerland Department of Anatomy, Faculty Hospital, Hradec Králové

One of the most common problems in dental implantology is insufficient alveolar bone in the posterior region of the upper jaw due to maxillary sinus pneumatization. In these cases the sinus lift procedure is used to achieve the necessary bone dimensions. Autogenous bone is the most common augmentation material used for this procedure. However, this is the reason for the relatively large invasiveness of this operation. The aim of this project is to reduce the invasiveness of the sinus lift procedure by using only non-autogenous material. This modified method will be performed under local anesthesia and without hospitalization. The authors want to judge the most adequate type of implants for use in the augmented bone

In June 2004 the paper "Shortening of the healing period of implants Impladent with a bioactive surface" was published (Quintessenz 13, 2004, 6: 34-38). In the year 2004 thirty-two sinus lift operations were performed with five types of augmentation materials. The dental implants were inserted to 35 patients. 8 CT scans of the augmented bone were carried out and 12 biopsies (from 15 planned) of the augmented bone were harvested. A panoramic X-ray was performed on all the operated patients before operating. In the year 2005 the authors will finish the harvesting of the bone and implantations of dental implants. A histomorphometric examination of the samples will be realized. The results will be statistically processed, interpreted and published.

Project was supported by the Ministry of Health Grant Agency, Czech Republic, No. NK/7711-3

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**Title of the research project:** Incorporation of smoking negative consequences in the oral cavity into the dental curriculum at the Medical Faculty in Hradec Králové

**Grant Agency:** Ministry of Education

**Project Number:** 1769/2004

**Principal Researcher:** Radovan Slezák

**Joint Researchers:** Aleš Ryška, Katarína Kosorínová

**Starting date:** 1. 1. 2004

**Duration (years):** 1

**Funds allocated for project - total in Czech crowns:** 81000

**Summary of 2004 results**

**Title of the presentation:** Incorporation of smoking negative consequences in the oral cavity into the dental curriculum at the Medical Faculty in Hradec Králové

**Authors:** Radovan Slezák (1), Aleš Ryška (2), #Katarína Kosorínová (1)

Medical Faculty, Charles Univ., Hradec Králové, Dept. of Dentistry (1), Fingerland's Dept. of Pathology (2), #undergraduate student

Smoking habits or tobacco abuse reveal a lot of negative consequences for oral health. These problems are not implemented in the current curriculum as a unique theme yet, but nearly all undergraduate students and all dentists will be confronted with various clinical signs and symptoms of oral diseases and disturbances associated or modified by the smoking and tobacco abuse.

The aim of the project was to create a complex programme dealing with all known risks and negative influences of smoking habits on soft and hard oral tissues (oral mucosa, gingiva and other periodontal tissues, tooth structures), and salivary glands, as well. The result is a new virtual programme "SMOKING AND ORAL CAVITY" accessible recently on the intranet of the Medical Faculty in Hradec Králové. The programme will be incorporated into the current "dental" curriculum since the summer term 2004/2005 in the 5th year of the study of dentistry and recommended for students of general medicine during the 4th year of the study in association with the subject "Dentistry".

A CD version and/or publication(s) will be done in future, too. The knowledge about risks and oral pathology associated with tobacco abuse would be very useful for the prevention, diagnosis and treatment of various oral diseases in the practice of all newly graduated dentists.

Project was supported by Ministry of Education, No 1769/2004.

**Address for correspondence:** R. Slezák, Dept. of Dentistry, Teaching Hosp., Medical Faculty in Hradec Králové, Charles Univ. in Prague, Czech Republic, slezak@lfhk.cuni.cz

**Title of the research project:** Angiogenesis Inhibitors In Multiple Myeloma

**Grant Agency:** Ministry Of Health

**Project Number:** NR/8076-3

**Principal Researcher:** Miroslav Penka

**Joint Researchers:** Lukáš Smolej, Luděk Pour, Vladimír Maisnar, Ctirad Andrýs, Petra Benešová, Roman Hájek

**Starting date:** 1.1.2004

**Duration (years):** 3

**Funds allocated for project - total in Czech crowns:** 1900000

**Summary of 2004 results**

**Title of the presentation:** Plasma concentrations of vascular endothelial growth factor and basic fibroblast growth factor in peripheral blood and bone marrow of patients with multiple myeloma.

**Authors:** Lukáš Smolej (1), Luděk Pour (4), Ctirad Andrýs (2), Petra Benešová (3), Vladimír Maisnar (1), Roman Hájek (4), Miroslav Penka (5).

Charles Univ.Teaching Hospital Hradec Králové: (1) Dept. of Clin.Haematology, (2) Institute of Clin. Immunology and Allergology, (3) Fingerland Dept. of Pathology  
Masaryk Univ.Teaching Hospital Brno: (5) Internal Haematooncology Dept, (6) Dept. of Clin.Haematology

Angiogenesis is nowadays considered one of the key porocesses in the pathogenesis of multiple myeloma (MM). Increased angiogenesis in MM has been identified as powerful negative prognostic factor. We investigated plasma concentrations of key angiogenic cytokines vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) in 45 peripheral blood plasma samples and 34 marrow plasma samples from patients with newly diagnosed MM. Significantly increased concentrations of both VEGF and bFGF in bone marrow plasma compared to peripheral blood were found ( $p=0,0424$  and  $<0,0001$ , respectively, Mann-Whitney U test). We also found significant increase in blood bFGF concentrations compared to control group consisting of 20 healthy volunteers ( $p=0,0003$ , Mann-Whitney U test). We confirmed increase in angiogenic cytokines in peripheral blood and marrow plasma of MM patients. .More patients are needed for detailed statistical evaluation including prognostic significance. However, these preliminary findings clearly warrant further investigation.

This project was supported by Ministry Of Health Grant Agency, NR/8076-3

***Address for correspondence:*** Lukáš Smolej, 2<sup>nd</sup> Department of Internal Medicine,  
Department of Clinical Haematology, Charles University Hospital, Sokolská 581, Hradec  
Králové, 500 05, Czech Republic

**Title of the research project:** Nutrition and Alzheimer Disease

**Grant Agency:** Ministry of Health

**Project Number:** NR7964-3

**Principal Researcher:** Luboš Sobotka

**Joint Researchers:** Zdeněk Zadák, Dagmar Solichová, Radomír Hyšpler, Miroslava Navrátilová

**Starting date:** 1.1.2004

**Duration (years):** 3

**Funds allocated for project - total in Czech crowns:** 564000

**Summary of 2004 results**

**Title of the presentation:** Nutritional status assessment in the elderly patients with Alzheimer disease.

**Authors:** L. Sobotka, \*M. Navrátilová, R. Hyšpler, Z. Zadák, Department of Metabolic Care and Gerontology, Medical Faculty, Charles University, Hradec Kralove, Czech Republic, \*Department of Psychiatry, Faculty Hospital, Brno, Czech Republic

The Mini Nutritional Assessment (MNA), is useful tool for early recognition of malnutrition especially in elderly populations. Alzheimer disease patients (AD) are at increased risk of malnutrition. The aim of present study was to assess the possibility of MNA to diagnose malnutrition in elderly patients with dementia of AD origin or vascular dementia (VD). The study was provided on 163 institutionalized elderly subjects. The patients weighed and height was recorded; skinfold thickness was measured above left triceps muscle. Spontaneous nutritional intake was measured during three working days and one weekend day. Data were compared by t-test and regression analysis.

106 patients suffered from AD and 57 patients had VD. BMI lower than 22 kg.m<sup>-2</sup> was recorded in 43.3% of AD patients and in 25% of VD patients. BMI was significantly lower in AD patients than in patients with VD (25.5 ± 5.0 vs. 23.0 ± 3.6 kg.m<sup>-2</sup> - p<0.001). Triceps skinfold thickness was also lower in AD patients (1.38 ± 0.6 vs. 1.7 ± 0.85 cm - p<0.01). Spontaneous food intake was only moderately lower in AD patients than in VD, however, the difference was statistically significant (9899 ± 2844 vs. 10877 ± 2383 kJ/day - p<0.05). MNA correlated significantly with food intake both in AD group (p<0.01) as well as in VD group (p<0.01).

It can be concluded from our study that patients with AD are more frequently malnourished than patients with VD. MNA seems to be good predictor of malnutrition in both groups of patients.

Project was supported by IGA MZ CZ, No NR7964-3.

**Address for correspondence:** Luboš Sobotka, prof., M.D.,Ph.D., Dept. of Metabolic Care, and Gerontology, Teaching Hospital, 500 05 Hradec Králové, Czech Republic

**Title of the research project:** Contrast-enhanced Magnetic Resonance Imaging versus SPECT Thallium Scintigraphy in the Detection of Myocardial Viability. Prospective Comparative Study

**Grant Agency:** Ministry of Health

**Project Number:** NA/7248-3

**Principal Researcher:** Miroslav Solar

**Joint Researchers:** Jan Zizka, Ludovit Klzo, Jiri Dolezal, Jaroslav Vizda, Jiri Ceral, Jiri Kvasnicka, Vladimir Lonsky, Pavel Zacek

**Starting date:** 1.1.2002

**Duration (years):** 3

**Funds allocated for project - total in Czech crowns:** 1500000

#### **Summary of 2004 results**

**Title of the presentation:** Contrast-enhanced Magnetic Resonance Imaging versus SPECT Thallium Scintigraphy in the Detection of Myocardial Viability. Prospective Comparative Study

**Authors:** Miroslav Solar (1), Jan Zizka(2), Ludovit Klzo(2), Jiri Dolezal(3), Jaroslav Vizda(3), Jiri Ceral(1), Jiri Kvasnicka (1), Jaroslav Āintĕra (4) Vladimir Lonsky(5), Pavel Zacek(5)

(1)1st. Department of Internal Medicine, (2)Department of Radiology, (3)Department of Nuclear Medicine and (5)Department of Cardiac Surgery University Hospital Hradec Kralove (4)Institute of Clinical and Experimental Medicine, Prague

Background - The aim of study was to compare contrast-enhanced magnetic resonance imaging (CE-MRI) to single-photon emission tomography using Thallium-201chloride (SPECT TI) in the detection of myocardial viability.

Methods - Patients with chronic coronary artery disease and systolic dysfunction defined by ejection fraction (EF)  $\leq 45\%$  were included. CE-MRI was performed using Inversion Recovery Turbo FLASH (fast low-angle shot) sequence and 4-hours rest redistribution protocol was used for SPECT TI.

Results -Total number of 40 patients was included and 32 of them underwent follow-up exam after revascularization. The concordance in the myocardial viability assessment between the two methods was noted in 1065 (78,3%) segments, that in resulted in moderate agreement only (kappa value 0,336). The EF increased by 5,5 ( $\pm 7,31$ ) % after revascularization, but the relation between the amount of dysfunctional viable myocardium and change of EF after revascularization was very weak and not statistically significant in both methods studied  
Conclusion - Moderate agreement in the myocardial viability assessment between CE-MRI and SPECT TI was observed. We did not prove the usefulness of any of the methods studied for the prediction of improvement of EF after revascularization.

**Address for correspondence:** Miroslav Solar, I.interni klinika, Fakultni nemocnice, Hradec Kralove, Czech republic, solarmir@seznam.cz



**Title of the research project:** Mechanisms of aging-the application of monolithic column technology in HPLC analysis of biologically active substances in gerontology

**Grant Agency:** Ministry of Health

**Project Number:** NR/8048-3

**Principal Researcher:** Dagmar Solichová

**Joint Researchers:** Vladimír Bláha, Bohuslav Melichar, Petr Solich, Miloš Klejna, Jiří Zajíc, Zdeněk Zadák, Lucie Nováková

**Starting date:** 1.1.2004

**Duration (years):** 3

**Funds allocated for project - total in Czech crowns:** 1400000

**Summary of 2004 results**

**Title of the presentation:** C18 monolithic rod columns and conventional C18 particle-packed columns in liquid chromatographic determination of Estrogel and Ketoprofen gel

**Authors:** Lucie Nováková (1), Ludmila Matysová (1), Dagmar Solichová (2), Michael A. Koupparis (3), Petr Solich (1)

Dept. of Analytical Chemistry, Faculty of Pharmacy, Charles University, Hradec Králové (1),

Dept. of Metabolic Care and Gerontology, Teaching Hospital, Hradec Králové (2),

Laboratory of Analytical Chemistry, Chemistry Dept., University of Athens, Greece (3)

Nowadays the most challenging trend in liquid chromatography (and for the near future as well) is the development of new sorbents, which are able to separate efficiently complicated substances, e.g. polar or basic. Such sorbents should be able to work in a wide pH range and should perform analysis as fast as possible while sufficient separation, method sensitivity and selectivity remain unaffected.

One of these novel types of sorbents is a monolithic silica (analytical columns Chromolith™ Merck). They mark out different structure comparing to conventional silica. While the typically used columns are filled with small silica spherical particles, monolithic columns contain a special silica (or another material), which is not formed by particles. They are made by sol-gel technology, which enables formation of highly porous material, containing macropores and mesopores in its structure. The performance of monolithic HPLC columns Chromolith™ (made by Merck, Germany) and conventional C18 columns Discovery (Supelco, Sigma-Aldrich, Prague, Czech Republic) was tested and the comparison for two topical preparations Ketoprofen gel and Estrogel gel was made. It was proved that monolith columns, due to their porosity and low back-pressure, can save analysis time by about a factor of three with sufficient separation efficiency. Thus, for example 11 min long analysis can be performed in 4 min with comparable results.

Project was supported by the IGA Ministry of Health Czech Republic, No. NR/8048-3.

**Address for correspondence:** Dagmar Solichová, Dept. of Metabolic Care and Gerontology, Teaching Hospital, 500 05 Hradec Králové, Czech Republic

**Title of the research project:** The relation of morphology of pulmonary veins to atrial fibrillation, with particular attention to isolated atrial amyloid

**Grant Agency:** Ministry of Health

**Project Number:** NA/7592-3

**Principal Researcher:** Ivo Šteiner (1)

**Joint Researchers:** Iva Kholová (1), Jiří Kvasnička (2), Petra Hájková (1)  
Department of Pathology (1) and 1st. Department of Internal Medicine (2), Faculty Hospital, Hradec Králové

**Starting date:** 1 January 2003

**Duration (years):** 3

**Funds allocated for project - total in Czech crowns:** 1934000

**Summary of 2004 results**

**Title of the presentation:**

**Authors:**

Atrial fibrillation is the most common supraventricular arrhythmia, moreover with an increasing prevalence. Attacks of the arrhythmia are triggered by ectopic activity originating mostly from the pulmonary veins. Left atrial myocardium frequently extends onto pulmonary veins (so called myocardial sleeves). The myocardial "sleeves" have been histologically examined for the presence, quantity, and character of isolated atrial amyloid - one of the "senile" amyloids.

A hypothesis is put forward that amyloidosis of pulmonary veins may play a role in pathogenesis of atrial fibrillation.

During the second year of the project 40 necropsy specimens of heart + pulmonary veins from patients both with atrial fibrillation and negative controls were examined for the presence and character of amyloid by means of histochemical (Saturn red) and imunohistochemical (atrial natriuretic peptide; transthyretin) staining methods. The total number of specimens examined by now is 80.

In addition to amyloid we have started to search for fibrosis (scarring) in the myocardial "sleeves" The incidence of scarring appears much higher than generally appreciated so far. After completing examination of the final number of 100 hearts evaluation of both amyloidosis and scarring as well as clinico-pathological correlation will take place.

Publication: I. Kholova, H.W.M. Niessen: Amyloid in the cardiovascular system: a review. J. Clin Pathol 2004 (in. print).

**Address for correspondence:** Prof. I. Steiner, M.D., Dept. of Pathology, Faculty Hospital, 500 05 Hradec Králové, Czech Republic, steiner@lfhk.cuni.cz



**Title of the research project:** Study on echographical evaluation of diastolic function in rabbit

**Grant Agency:** Ministry of Education

**Project Number:** 1776/G3/04

**Principal Researcher:** Martin Štěrba

**Joint Researchers:** Vladimír Geršl

**Starting date:** 1.1.2004

**Duration (years):** 1

**Funds allocated for project - total in Czech crowns:** 122000

**Summary of 2004 results**

**Title of the presentation:** Echo-doppler evaluation of diastolic function in rabbit - technical consideration and a pilot study of predictive value for early diagnosis of daunorubicin induced cardiotoxicity.

**Authors:** Martin Štěrba, Olga Popelová, Vladimír Geršl

Charles University in Prague, Faculty of Medicine in Hradec Králové, Department of Pharmacology.

The study was focused on 1/ a feasibility of the echo-doppler evaluation of diastolic function and 2/ a pilot estimation of a predictive value of this measurement for daunorubicin-induced cardiotoxicity in rabbits. Chinchilla male rabbits (n=20) were used in this study. At first the acquisition of apical four-chamber view was obtained and standardized. Sample volume was placed between the leaflets of mitral valve and PW (HPRF) Doppler measurement was performed. Under ketamine anaesthesia (50 mg/kg), it was impossible to distinguish typical biphasic character of the Doppler record (only E-wave was visualised). During combined anaesthesia (ketamine 50 mg/kg, xylazine 2 mg/kg) it was possible to evaluate all desirable parameters (E, A, E/A, acceleration time, deceleration time). Heart rate was determined to be a principal limiting factor. Further measurements were performed once weekly, 10 weeks, both under ketamine (n=5) and combined (n=5) anaesthesia. The measurement was reasonably reproducible (e.g. E-ket and E-combin. oscillated in a range 0.80-0.93 m/s and 0.53-0.59 m/s, resp.). This approach was further used in rabbits (n=5) with daunorubicin administration in a standard protocol for induction of chronic cardiotoxicity (3 mg/kg, i.v., once weekly, 10 weeks). No significant changes in evaluated parameters were observed in the daunorubicin group either in comparison with the initial values or in comparison with the control group with combined anaesthesia (E/A index between 1.24 and 1.55). Thus, Doppler evaluation of diastolic function does not seem to have a significant predictive value for daunorubicin-induced cardiotoxicity in rabbits. Supported by a grant FRVŠ 1776/G3/04.

**Address for correspondence:** Martin Štěrba, Department of Pharmacology, Faculty of Medicine in Hradec Králové, Charles University in Prague, Šimkova 870, 500 38 Hradec Králové, Czech Republic. E-mail: sterbam@lfhk.cuni.cz.



**Title of the research project:** Innovation in pre-clinical training of periodontology for students  
of dentistry

**Grant Agency:** Ministry of Education

**Project Number:** 996/2004

**Principal Researcher:** Maher Taha

**Joint Researchers:** Ivo Dřízhal

**Starting date:** 1. 1. 2004

**Duration (years):** 1

**Funds allocated for project - total in Czech crowns:** 193000

**Summary of 2004 results**

**Title of the presentation:** Innovation in pre-clinical training of periodontology for students of dentistry

**Authors:** Maher Taha, Ivo Dřízhal

Fac. Med., Charles Univ., Hr. Králové: Dept. of Dentistry

The periodontal examination and removal of sub- and supragingival calculus belong to the first training of the students in our clinic and it is the first contact between student and patient. The aim of this project is to acquaint the students with the techniques of removing the calculus on models during pre-clinical training. Until now the students have had this subject in the 3rd year and directly in the patient's mouth. Therefore it is reasonable at first to demonstrate and perform this on the models to prevent mistakes, errors and prolonged treatment. We shall use for this goal, special periodontal models with synthetic calculus, curettes, probes, polishing sets and other necessary instruments. These models are compatible with the existing phantoms in our clinic. The result of this project is innovation in the dental curriculum of pre-clinical dentistry. In the syllabus of the 2nd year a new subject "pre-clinical periodontology" will be added in the summer term (15 hours). 6 hours practice include: 1) Use of scalers and curettes for supragingival calculus removal. 2) Scaling – subgingival calculus removal. 9 hours lectures include: 1) Basic instruments for periodontal examination and treatment and their maintenance. 2) Periodontal examination. 3) Classification of periodontal diseases. The periodontal models will be accessible to every student from the higher years according to their own request or to the decision of his teacher. Due to this training the student will be prepared and capable to use all the required instruments properly.

Project was supported by the Ministry of Education, No 996/2004.

**Address for correspondence:** M. Taha, Dept. of Dentistry, Charles University in Prague, Faculty of Medicine and Teaching Hospital in Hradec Králové, Sokolská 581, 500 05 Hradec Králové, Czech Republic

**Title of the research project:** Interactive communication technology in the teaching of Obstetrics and Gynaecology

**Grant Agency:** Ministry of Education

**Project Number:** 905 A

**Principal Researcher:** Jindřich Tošner

**Joint Researchers:** Ivo Kalousek

**Starting date:** 19.2.2004

**Duration (years):** 1

**Funds allocated for project - total in Czech crowns:** 1 181 000

**Summary of 2004 results**

**Title of the presentation:** Modern trends in the teaching of Obstetrics and Gynaecology

**Authors:** Jindřich Tošner, Ivo Kalousek

Faculty of Medicine, Charles University, Hradec Králové, Department of Gynaecology and Obstetrics

The aim of the project was to introduce modern technology to teaching of Obstetrics and Gynecology to improve possibility of practical training and give to students full access to internet which should be used interactively during lectures. Within the framework of the project we have set up computer workstation for 5 students connected in network with copying equipment and server reserve where large study materials (films) can be stored and watched during student afternoon and night duties. Internet access is basic for preparation of writing esseys as a part of the state exam. Digital professional camera allows us to prepare own teaching films from obstetric hall and operating theater. Practical training classroom was equipped with hysteroscopic diagnostic trainer, minimal access therapy trainer with gynae dissection pad, episiotomy trainer, clinical female pelvic trainer, palpation model for Pawlik maneuvers, birthing station simulator, childbirth and gynecological simulator. Lecture hall technology allows us to present lectures with the help of Interwrite meeting software, with possibility of DVD presentations and videoconferencing. For lecturers full featured digital presenter LUMENS make presentations easier and gives wide scale of teaching possibilities with the use of books and three dimensional subjects. Perfect teaching technology save a time of teachers, allow to students use a time of study more effectively, gives higher possibility to individual approach to every student but can not replace effort, knowledge and educational ability of the teacher.

Project was supported by the grant of Ministry of Education of Czech Republic, No 905 A/2004

**Address for correspondence:** J.Tošner, Dept. of Obstetrics and Gynecology, Teaching Hospital, Sokolská 581, CZ-50005 Hradec Králové, Czech Republic

**Title of the research project:** Improvement of the practical instruction in prosthetic technology

**Grant Agency:** Ministry of Education

**Project Number:** 997/F3/a

**Principal Researcher:** Dagmar Vahalová

**Joint Researchers:** Jiří Bittner, Lenka Vavříčková

**Starting date:** 1. 1. 2004

**Duration (years):** 1

**Funds allocated for project - total in Czech crowns:** 178000

**Summary of 2004 results**

**Title of the presentation:** Improvement of the practical instruction in prosthetic technology.

**Authors:** Dagmar Vahalová, Jiří Bittner, Lenka Vavříčková

Fac. Med., Charles Univ., Hr. Králové: Dept. of Dentistry

The practical preclinical dental instruction in prosthetic technology in the summer term of the second schoolyear has been enriched with the all - veneer cast metal crown fabrication. Students exercise not only the preparation of a tooth to achieve this type of crown but all necessary laboratory stages. They shape the wax pattern of this crown using the wax - up technique, make the casting mold from the refractory investment material, cast the crown from appropriate dental alloy, polish it and adapt it on the prepared tooth. They familiarize themselves practically with the material properties taught theoretically during the lectures in prosthetic technology. Thus they are able to compare the properties of the best high - strength stone to the model resin, learn the right handling with the cast inlay wax, investment materials, perform the casting procedure and so on. The practicals are held in the separated students' teaching laboratory equipped with all necessary instruments and devices.

Project was supported by Ministry of Education, No 997F3/a.

**Address for correspondence:** D. Vahalová, Dept. of Dentistry, Charles University in Prague, Faculty of Medicine and Teaching Hospital in Hradec Králové, Sokolská 581, 500 05 Hradec Králové, Czech Republic.

**Title of the research project:** Disorders of intestinal permeability following chemotherapy of ovarian carcinoma and urinary neopterin as an indicator of systemic immune activation

**Grant Agency:** Ministry of Health

**Project Number:** NR 8156

**Principal Researcher:** Emanuela Vobořilová

**Joint Researchers:**

Bohuslav Melichar

Radomír Hyšpler

Dagmar Solichová

Josef Dvořák

Alena Tichá

Jiří Špaček

**Starting date:** 01.01.2004

**Duration (years):** 3

**Funds allocated for project - total in Czech crowns:** 1141000

**Summary of 2004 results**

**Title of the presentation:** Gastrointestinal permeability in patients treated by paclitaxel/platinum combination chemotherapy

**Authors:** B Melichar, E Voborilova, R Hyšpler, D Solichová, S Melicharová, J Dvořák  
Departments of Medicine, Oncology/Radiotherapy, Gynecology/Obstetrics and Gerontology/Metabolic Care, Charles University Medical School, Hradec Králové

Paclitaxel/platinum combination is a standard first-line chemotherapy in patients with advanced epithelial ovarian carcinoma. Although gastrointestinal toxicity is one of the most common side effects of cytotoxic drugs, the diagnosis and assessment of this frequent complications relies mostly on anamnestic data. Measurement of gastrointestinal permeability offers an opportunity for objective assessment of the presence and extent of the disorders of barrier function of the intestinal mucosa associated with the administration of cytotoxic agents. This non-invasive test involves ingestion of defined quantities of mono- and disaccharides and timed urine collection, with the results expressed as disaccharide/monosaccharide ratio. Preliminary data on 9 patients treated by paclitaxel/platinum chemotherapy indicate little effect of these cytotoxic drugs on gastric (measured as saccharose/mannitol ratio) and intestinal (measured as lactulose/mannitol ratio) permeability. A marked increase in both lactulose/mannitol and saccharose/mannitol ratios has been observed so far only in 2 out of 9 patients, both of whom have received previous chemotherapy and had marked myelosuppression after the administration of paclitaxel/platinum chemotherapy. This lack of a significant increase in gastrointestinal permeability after paclitaxel/platinum chemotherapy is in agreement with limited gastrointestinal toxicity of this regimen. At this moment, a total of 22 patients have been enrolled (including patients treated by second line regimens with gemcitabine and topotecan), and enrollment of additional patients as well as data collection are ongoing. Other analyses will evaluate the effect of chemotherapy on urinary neopterin, an indicator of systemic immune activation, and on serum retinol and alpha-tocopherol concentrations.

**Address for correspondence:** Bohuslav Melichar M.D., Ph.D. Departments of Medicine and Oncology/Radiotherapy, Charles University Medical School, 500 05 Hradec Králové, Czech Republic

**Title of the research project:** Tissue factor plasma level in patients with acute coronary syndrome and with stable coronary artery disease

**Grant Agency:** Ministry of Health

**Project Number:** NR/8131-3

**Principal Researcher:** Jan Vojáček, MD, DrSc, FACC, FESC

**Joint Researchers:** Professor Malý Jaroslav, MD, CSc, Bis Josef MD, Hodač Tomáš MD, Blažek Martin, MD

**Starting date:** Jan 1, 2004

**Duration (years):** 3

**Funds allocated for project - total in Czech crowns:** 1473000

**Summary of 2004 results**

**Title of the presentation:** Circulating Metalloproteinases, soluble Ligand CD40 (sLCD40), soluble tissue factor (sTF) or high sensitivity CRP (hs CRP) as a marker of Acute Coronary Syndrome ?

**Authors:** Hodač T, Bis J, Vojáček J, Blažek J, Malý J.

Active lesions in patients with acute coronary syndromes are multifocal. Activation of multiple sites in coronary vascular bed may be dependent on circulating cellular elements (i.e. platelets, monocytes, polymorphonuclear leukocytes) as well as on some humoral mechanisms (as documented for metalloproteinases measured as Pregnancy Associated Plasma Proteins A – PAPP-A). At the present, markers of myocardial necrosis (troponins, CK MB mass) or inflammation (hs CRP) are used to diagnose and stratify patients with acute coronary syndromes.

The possibility to identify patients at risk for the development of circulating cells interaction is evaluated. The amount of platelet – monocyte interaction is assessed by sLCD40 and its level is correlated to the level of metalloproteinases 2, 3 and 9, metalloproteinases inhibitor, sTF and tissue factor pathway inhibitor. The measurement is performed in the blood obtained from the ostium of left coronary artery, coronary sinus as well as from peripheral vein for all parameters. The aim of the proposed research project is to compare circulating metalloproteinases 2, 3 and 9, sLCD40 and sTF levels in patients with chronic stable coronary artery disease and in patients presented with acute coronary syndromes.

**Address for correspondence:** Vojáček J, MD, DrSc, FESC, FACC, Dept. Medicine I, University Hospital Hradec Králové 500 05, Sokolská 581

**Title of the research project:** Treatment of head and neck cancer by intensity-modulated radiotherapy with the use of simultaneous integrated boost

**Grant Agency:** Charles University

**Project Number:** 137/2004

**Principal Researcher:** Milan Vošmik

**Joint Researchers:** Jiří Petera, Karel Odrážka, Milan Zouhar, Zdeněk Zoul, Jan Vokurka

**Starting date:** 1.1.2004

**Duration (years):** 3

**Funds allocated for project - total in Czech crowns:** 270000

#### **Summary of 2004 results**

**Title of the presentation:** Treatment of head and neck cancer by intensity-modulated radiotherapy with the use of simultaneous integrated boost: acute toxicity evaluation

**Authors:** Milan Vošmik (1), Jiří Petera (1), Karel Odrážka (1), Milan Zouhar (1), Petr Kordač (2), Josef Dvořák (1), Zdeněk Zoul (1), Martin Doležel (1), Miloslava Vaculíková (1), Jana Bedrošová (1)

Charles University Medical School nad Teaching Hospital: Oncology and Radiotherapy Department (1), Department of Otolaryngology, Head and Neck Surgery (2), Sokolská 581, 500 05 Hradec Králové

**Introduction:** Authors prepared treatment protocol for irradiation of head and neck cancer by intensity-modulated radiotherapy (IMRT) with the use of simultaneous integrated boost. The basis of protocol is the irradiation in 30 fractions with total dose: 66 Gy to the region of macroscopic tumor, 60 Gy to the region of high-risk subclinical disease and 54 Gy to the region of low-risk subclinical disease. Acute toxicity of the treatment was evaluated.

**Materials and methods:** Between December 2003 and December 2004, 15 patients with carcinoma of different locations of head and neck region were irradiated. 2 patients with nasopharyngeal carcinoma underwent concurrent chemotherapy (CDDP weekly). Acute toxicity was evaluated according to RTOG toxicity scale for skin, mucous membrane, salivary glands, pharynx and esophagus and larynx.

**Results:** All 15 patients finished the therapy without urgency of interruption due to acute toxicity. No patient experienced Grade 4 toxicity. More severe toxicity was observed in patients with concurrent chemotherapy, however Grade 3 toxicity at most.

**Conclusion:** IMRT with the use of simultaneous integrated boost and mentioned fractionation schedule is a therapy with acceptable toxicity.

Project is supported by the Charles University Grant Agency, No 137/2004

**Address for correspondence:** M. Vošmik, Charles University Medical School nad Teaching Hospital in Hradec Králové, Oncology and Radiotherapy Department, Sokolská 581, 500 05 Hradec Králové



**Title of the research project:** Innovation - quality raising in orthodontic education

**Grant Agency:** Ministry of Education

**Project Number:** 998/2004

**Principal Researcher:** Zuzana Weberová

**Joint Researchers:**

**Starting date:** 1.1. 2004

**Duration (years):** 1

**Funds allocated for project - total in Czech crowns:** 109000

**Summary of 2004 results**

**Title of the presentation:** Innovation - quality raising in orthodontic education

**Authors:** Zuzana Weberová

Fac. Med., Charles Univ., Hr. Králové: Dept. of Dentistry

The aim of orthodontic treatment is to produce improved function by the correction of irregularities and to create not only greater resistance to disease but also to improve personal appearance. The general dentist has the crucial role in the initiation of orthodontic treatment. For this reason a thorough orthodontic assessment of the occlusion should be a routine for every patient. During the examination of the patient, the assessment of the incisal relationship and underlying skeletal pattern provides key information for determining the general nature of the treatment to be provided. Where the dental irregularity and the underlying skeletal pattern is more severe, visualisation of proposed tooth movements is required. This cannot be provided without tempromandibular joint function simulation. Articulators are very useful for this purpose. It is elementary for dentistry students to improve their skills in transferring of the incisor relationship to the simulator and to mount the model to the articulator. Furthermore these knowledges ensure proper interdisciplinary treatment planning, too. The general dentist is a member of the interdisciplinary team which should provide the best as possible treatment for the developing occlusion or reconstruction of adult denture. Treatment planning and visualisation of proposed teeth movements require the best as possible simulation which cannot be provided without extended training in situation transfer and model mounting to the articulator. The aim of this project was raising the quality of undergraduate orthodontic education, which includes several theoretical and practical hours in situation transfer and model mounting to the articulator.

The project was supported by Ministry of Education, No 998/2004.

**Address for correspondence:** Z. Weberová, Dept. of Dentistry, Charles University in Prague, Faculty of Medicine and Teachnig Hospital in Hradec Králové, Sokolská 581, 500 05 Hradec Králové, Czech Republic

**Title of the research project:** The changes in the metabolism of cholesterol and its precursors in the patients in critical care

**Grant Agency:** Ministry of Health

**Project Number:** NB/6589-3

**Principal Researcher:** Zdeněk Zadák

**Joint Researchers:** Radomír Hyšpler, Eduard Havel, Vladimír Černý, Tomáš Dědek, Vladimír Palička, Jan Krejsek, Martina Loudová, Luboš Sobotka

**Starting date:** 1.1.2003

**Duration (years):** 3

**Funds allocated for project - total in Czech crowns:** 810000

**Summary of 2004 results**

**Title of the presentation:** The changes in the metabolism of cholesterol and its precursors in the patients in critical care

**Authors:** Zadák Z. (1), Hyšpler R. (1), Havel E. (2), Černý V. (3), Dědek T. (2), Palička V. (4), Krejsek J. (5), Loudová M. (5), Sobotka L. (1)

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Cholesterol and precursors of cholesterol synthesis, important structural compounds and metabolic mediators are invariably and markedly depleted in critical patients.

Deficiency of cholesterol and cholesterol related metabolites has been monitored by means of plasma lanosterol and lathosterol concentrations in severely ill and polytraumatised patients. This phenomenon is accentuated in patients treated by total parenteral nutrition (TPN) and in addition accumulation of phytosterols above all sitosterol and campesterol has been found in this situation. Origin of phytosterols is undoubtedly from certain intravenous lipid emulsions rich in campesterol and sitosterol used in long term TPN. Accumulation of phytosterols in the organism is undesirable event, which is still clinically underestimated. Fundamental question of this study is application of the cholesterol synthesis precursors as markers of disease and trauma severity and assessment of cholesterol and cholesterol synthesis precursors as conditionally essential nutrients in critical patients.

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**Title of the research project:** Effect of humic substances in vivo.  
Study of chemical and physical characteristics of humic substances and their biological activity, mechanism of effect on microorganisms, plant cells and animal cells in the dependence on the humic substances structure.

**Grant Agency:** Ministry of Industry and Trade      **Project Number:** FT-TA/038

**Principal Researcher:** Zdeněk Zadák

**Joint Researchers:** Radomír Hyšpler, Alena Tichá, Dagmar Solichová, Bohuslav Melichar, Petr Žďánský, Iveta Svobodová, Marie Mejtská, Jana Tilšarová, Jana Krejcarová, Marcela Vacková

**Starting date:** 1.1.2004

**Duration (years):** 5

**Funds allocated for project - total in Czech crowns:** 2100000

#### **Summary of 2004 results**

**Title of the presentation:** Effect of humic substances in vivo.

**Authors:** Zadák Z., Hyšpler R., Tichá A., Solichová D., Žďánský P., Melichar B.\*, Svobodová I., Mejtská M., Tilšarová J., Krejcarová J., Vacková M.

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During the first year of the project the methods to evaluate influence of humic substances on in vivo fermentation of soluble fibre in the colon and on intestinal barrier were developed.

The in vivo fermentation of fibre is determined using methane excretion into expired air. After ingestion of fibre expired air is collected in a special receptacle and methane content is determined by gas chromatography. The variation coefficient of an estimation is 2,05 %.

The lactulose-mannitol test was standardised in rats and is ready to be applied in humic substances effect evaluation. The conditions are: oral administration of an isotonic mixture of 50 mg of mannitol and 66 mg of lactulose, followed by collection of urine over 6 hours. As metabolites of mannitol are physiologically present in rat urine, the blank urine collection has to be performed before each test. The LA/MA ratio test results are 0,21 (SD 0,035) in the group of six animals.

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