Under the Auspices of European Society of Pathology
(President: Prof. Fred T. Bosman)
and Academy of Medical Sciences of Croatia
(President: Academician Ž. Reiner)

19th LJUDEVIT JURAK INTERNATIONAL SYMPOSIUM
ON COMPARATIVE PATHOLOGY

MAIN TOPICS
PEDIATRIC PATHOLOGY

ADVANCES IN PATHOMORPHOLOGY
TECHNIQUES

CONFERENCE PAPERS
June 6-7, 2008
ZAGREB, CROATIA

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SUPPORTED BY THE CROATIAN MINISTRY OF SCIENCE, EDUCATION AND SPORTS,  
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LECTURES

NON-ALCOHOLIC FATTY LIVER DISEASE (STEATOHEPATITIS) IN CHILDREN

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Non-alcoholic fatty liver disease (NAFLD) comprises a spectrum of liver disorders eventually leading to cirrhosis. In children and adolescents, NAFLD is presently the most common cause of chronic liver disease and, therefore, poses a major public health problem. The risk of NAFLD is modulated by age, sex, ethnicity and body habitus. The diagnosis of NAFLD and non-alcoholic steatohepatitis (NASH) is established by liver pathology in conjunction with clinical information (serum tests, ultrasonography, CT, MRI). The histologic features of NAFLD range from simple steatosis, steatohepatitis with or without fibrosis, to cirrhosis. The morphological key features of NASH in adults include macrovesicular steatosis, hepatocyte ballooning with or without hyaline inclusions (MDBs) and pericellular fibrosis. In pediatric patients, two distinct morphological patterns are recognized. Type 1 NASH closely resembles the adult disease with the presence of steatosis, ballooning hepatocyte degeneration and/or perisinusoidal fibrosis, whereas type 2 NASH is defined as the presence of steatosis with portal inflammation and portal fibrosis in the absence of hepatocyte ballooning and perisinusoidal fibrosis. The latter type is the most common pattern in children. These different morphological subtypes underline the heterogeneity of NAFLD and provide the rationale for further studies on the pathophysiology, molecular pathology and genetics of NAFLD in general and in children and adolescents in particular.
KIDNEY TUMORS IN CHILDREN

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Pediatric renal tumors were targeted by the International Society of Pediatric Oncology (SIOP) and National Wilms Tumor Study Group (NWTSG) for 4 decades with valuable progress in understanding the natural history of these tumors and an extraordinary success for both patients and clinicians. All renal tumors must first be registered on the National and International (Europe, North America) Renal Tumor Classification and Banking Protocol, followed by registration on 1 of 4 primary therapeutic protocols based on histology, stage, and molecular analysis. Wilms’ tumor (WT) comprises approximately more than three quarters of the renal malignancies of children and has to be the chief consideration in the differential diagnosis of any pediatric renal mass. However, a range of pediatric renal masses may be differentiated from WT on the basis of their both clinical-imaging and pathological features. WT is distinguished by vascular invasion and displacement of structures and is bilateral in approximately 10% of cases. Nephroblastomatosis occurs most often in neonates and is characterized by multiple bilateral subcapsular masses, while renal cell carcinoma is unusual in children except in association with von Hippel-Lindau syndrome and typically occurs in the 2nd decade. Among very different histological types, a careful pathological work-up should be made on congenital mesoblastic nephroma, which is the primary consideration in a neonate with a solid renal mass, multilocular cystic renal tumor, which is suggested by a large mass with multiple cysts and modest solid tissue, clear cell sarcoma that is characterized by its mesenchymal link and frequent skeletal metastases, and rhabdoid tumor that is distinguished by its typical both histological and ultrastructural features.
THE EPIDRUG 5-AZACYTIDINE AFFECTS
DEVELOPMENTAL PROCESSES IN VITRO AND IN VIVO

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5-azacytidine (5azaC) belongs to an emerging class of therapeutics sometimes called epidrugs, which are
acting at the level of epigenetics. Epigenetics implies regulation of gene expression through mechanisms such
as DNA methylation. 5azaC inhibits post-replication methylation by its incorporation into DNA, followed by
a change in gene expression. It has been used lately in the treatment of human malignancies, for activation of
fetal Hb gene expression in patients with sickle cell disease, or for promotion of cardiomyocyte differentia-
tion from mesenchymal stem cells in vitro for stem cell regenerative therapy of the heart. Our in vitro experi-
ments showed that 5azaC is able to directly affect the survival, proliferation and differentiation of the rat em-
bro-proper. During gestation in vivo it also affects pla-
centa, which is therefore partly responsible for its tera-
togenic effect. In the placenta, we were able to demon-
strate the stage-specific effect of 5azaC on the expres-
sion of cytosolic and membrane glycoproteins as well as
of the proliferating cell nuclear antigen (PCNA). 5azaC
increased PCNA expression in rat embryonic transplants
to the ectopic site. Not only fetal but also adult rat tes-
tis and its spermatogenesis were impaired by 5azaC.
These results indicate that epidrugs can cause serious
side effects.
THE CLINICAL PRESENTATION OF RHEUMATOID ARTHRITIS: THE RESULT FROM THREE SEPARATE PATHOGENETIC MECHANISMS IN ADULTS AND CHILDREN

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The clinical picture of rheumatoid arthritis (RA) is impressive indeed due to the phenomena of swelling, pain and stiffness; however, the specific severity of the disease develops because of progressive destruction of the joints accompanying the clinical symptoms described. In particular, RA assumes a malignant clinical course with a potentially fatal outcome if myocardial muscle, heart valves and blood vessels are involved in the disease process. According to our large-scale investigations (approximately 90,000 tissue samples referred to the ZRP since 1995, of patients suffering from a whole range of rheumatic disorders with respective detailed clinical data), we could define three different mechanisms responsible for the complete picture of RA:

1. an exudative-inflammatory process responsible for swelling, pain and stiffness;
2. a proliferative-destructive process responsible for joint destruction; and
3. an enzymatic collagenolytic process responsible for primary necrotizing of, e.g., myocardial muscle, blood vessels and sclera of the eye.

Consequently, RA is a more complicated process than it could be assumed from the basic clinically-immunologically understandable phenomena. The knowledge of the complex pathogenesis described while abandoning the popular monocausal inflammation concept are essential preconditions for a crucial progress in therapy of RA to expect in the future. On the other hand, completely different pathomechanisms determine the clinical picture of juvenile chronic arthritis (JCA). Only the seropositive type of JCA, followed by RA of adults, is associated with oncologic destruction of joints and primary extra-articular necroses. The basis of the typical joint process of oligoarticular subtypes is a creeping inflammation induced fibrosing process of the capsule tissue. An additional risk is uveitis that can lead to blindness.