

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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ZAGREB 6-7, JUNE 2008

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SUPPORTED BY THE CROATIAN MINISTRY OF SCIENCE, EDUCATION AND SPORTS, CROATIAN ACADEMY OF SCIENCES AND ARTS AND THE INSTITUTE FOR CLINICAL MEDICAL RESEARCH OF SESTRE MILOSRONICE UNIVERSITY HOSPITAL

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LECTURES

NON-ALCOHOLIC FATTY LIVER DISEASE (STEATOHEPATITIS) IN CHILDREN

H. Denk

Institute of Pathology, Graz Medical University, Graz, Austria

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 with-

out 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.





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C. Sergi

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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.

Acta Clin Croat, Vol. 47, No. 1 2008





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THE EPIDRUG 5-AZACYTIDINE AFFECTS DEVELOPMENTAL PROCESSESS *IN VITRO* AND *IN VIVO*

M. Vlahović¹, L. Šerman¹, M. Šijan¹, M. Ulamec^{1,2}, A. Katušić¹, G. Jurić-Lekić², A. Šerman^{1,4}, S. Marinović-Kulišić^{2,4,5}, N. Sinčić¹, D. Ježek², F. Bulić-Jakuš¹

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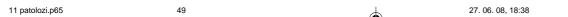
5-azacytidine (5azaC) belongs to an emerging class of therapeuticals sometimes called epidrugs, which are acting at the level of epigenetics. Epigenetics implies regulation of gene expression through mechanisms such as DNA methylation. 5azaC inhibits post-replication methylation by its incorporation 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 differentiation from mesenchymal stem cells *in vitro* for stem cell regenerative therapy of the heart. Our *in vitro* experiments showed that 5azaC is able to directly affect the

survival, proliferation and differentiation of the rat embryo-proper. During gestation *in vivo* it also affects placenta, which is therefore partly responsible for its teratogenic effect. In the placenta, we were able to demonstrate the stage-specific effect of 5azaC on the expression 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 testis and its spermatogenesis were impaired by 5azaC. These results indicate that epidrugs can cause serious side effects.





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Conference Papers





H. G. Fassbender

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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:

- 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.

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