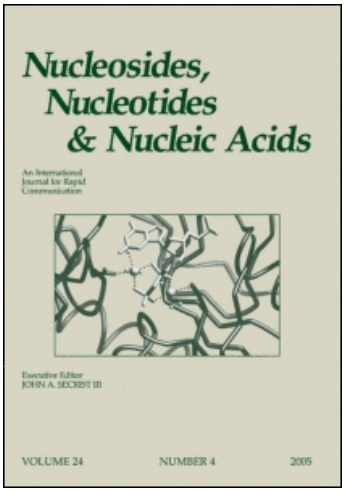

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Purine and Pyrimidine Metabolism: a Firm Basis for a Transformed Society

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PURINE AND PYRIMIDINE METABOLISM: A FIRM BASIS FOR A TRANSFORMED SOCIETY

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□ *Purines and pyrimidines form the backbone of DNA and RNA. Hence, modification of purine and pyrimidine metabolism can have serious effects on normal functioning of a subject. These aspects formed the main topics for an International and a European Series of meetings, dedicated to the metabolism in man. In order to streamline the organization of these meetings the European Society was transformed to an International society: the Purine and Pyrimidine Society (www.ppsociety.org). This special issue of* Nucleosides, Nucleotides and Nucleic Acids *highlights the last European meeting in Prague, focusing on inborn errors, cardiac diseases, inflammatory diseases, rheumatology, haematology, cancer, virology, genetic polymorphism, specific methodology, and, of course, metabolism. The meeting in Chicago in 2007 will be the first meeting of the Purine and Pyrimidine Society.*

Keywords Anticancer; Antimetabolites; Antiviral; Purine

Modification of purine and pyrimidine metabolism is the underlying cause for a number of serious inborn errors of metabolism, but knowledge arising from these defects is also the basis for successful treatment of various life-threatening and/or disabling diseases. These include cardiovascular diseases, infectious diseases, inflammatory diseases (e.g., rheumatoid arthritis), gout, and various malignancies, such as leukemia, non-small cell lung cancer, colon cancer, and pancreatic cancer. The study of purine and pyrimidine metabolism was the basis for a series of meetings starting in 1974 in Tel Aviv, Israel. In that decade a number of potentially disabling

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and life-threatening diseases were linked to serious disorders in metabolism, such as gout with a deficiency of hypoxanthine-guanine phosphoribosyl transferase, overactivity of phosphoribosyl pyrophosphate synthetase, and a severe combined immunodeficiency disease (SCID) with adenosine deaminase (ADA) deficiency. This last-named genetic defect was the first human disease in which gene therapy was initiated.

However, around that time a number of purine and pyrimidine analogs also were developed which became and still are the mainstay of some of the above-mentioned diseases, such as allopurinol for gout, uracil analogs such as 5-fluorouracil (5FU) for colon cancer, arabinosyl-cytosine (ara-C) for acute myeloid leukemia, 6-mercaptopurine (6MP) for childhood leukemia, azathioprine for inflammatory diseases, such as rheumatoid arthritis and inflammatory bowel disease. In the eighties there was another boost in the development of novel analogs, to be used as antiviral agents, such as gancyclovir and azidothymidine (AZT), and various anticancer agents, such as doxifluridine (later developed as capecitabine), and the deoxynucleoside analogs fludarabine, cladribine, and gemcitabine.

The development of these compounds would have been impossible without the chemistry and biology obtained by studies on inborn errors of metabolism. These studies gave an insight into the role and regulation of rate-limiting enzymes in purine and pyrimidine metabolism and how modification of these enzymes would enable the treatment of the above-mentioned diseases. However, these studies also suggested why some patients would respond to treatment or not. A number of different studies has shown that genetic polymorphisms are very important in determining why a patient will or will not respond to treatment. The characterization of the human (and later the mouse) genome gave an impetus to research on how the genetic basis of these diseases can be used to optimize treatment. So, despite decades of novel drug development one focus of the meeting of the European Society on the Study on Purine and Pyrimidine Metabolism in Man (ESSPPMM) in Prague, was on genetic polymorphisms in the metabolism of drugs developed in the fifties by Gertrude Elion and George Hitchings, who obtained a Nobel Prize for their work in this field. Their research indirectly led to the current boost in metabolomics, genomics and more recently also proteomics, a development they might have anticipated but not predicted. At the meeting in Prague (PP05) a number of studies dealt with predictive parameters for successful treatment, based on metabolic profiles. The characterization of the latter has been made possible by many technological developments, enabling the detection of mutations and genetic polymorphisms. Some studies have already demonstrated that the use of pre-treatment analysis of such polymorphisms will help to increase the response rate but also decrease the toxicity. Other

lectures in one session at the last meeting focused on the increasing clinical importance of the end product of purine metabolism in humans. Recent clinical and epidemiological studies have found that soluble uric acid has important biological roles. While it acts as an antioxidant, there is also evidence that uric acid has proinflammatory and proliferative effects on vascular smooth muscle cells and causes dysfunction of endothelial cells.These cellular mechanisms may translate into why uric acid has a role as a true cardiovascular risk factor, particularly for the development of hypertension and renal disease. Thus, the old debate as to whether symptomless hyperuricemia should be treated has been reawakened. Monitoring and controlling of hyperuricemia may be more important for physicians then previously thought. The use of oral febuxostat—a novel nonpurine selective inhibitor of xanthine oxidase seems to be more efficient then allopurinol.

Recent identification of the urate transporter 1 (URAT1) as a transporter molecule for urate reabsorption, a key regulator of blood urate levels, holds the promise for the development of new, more effective therapeutics for hyperuricemia. Despite these developments, the most prominent disease discussed in this series of meetings, the Lesch-Nyhan syndrome, associated with serious neurological disorders and gout, is still far from completely characterized. Unfortunately, the mechanisms by which a biochemical disorder leads to the neurological disorder is still unclear but some important concepts involving the mechanism of apoptosis were described at the PP05 meeting.

Collaboration between disciplines, which are always present at the biennial meetings of the ESSPPMM and at the triennial international meeting, has been shown to be essential. An example of the efficient, close collaboration between Society members was the formation of Data base of patients with inborn errors of purine and pyrimidine metabolism and joint substantial results of research within the EC project BMH4-CT98-3079 ("European Structure for Coordination of Research and Diagnosis of Inherited Purine and Pyrimidine Disorders") involving 17 European countries. The strength of the ESSPPMM and the international meetings is that they offer the possibility to provide this interaction between disciplines and within disciplines. Therefore, it was thought, and agreed after discussion by the majority of the members of Scientific Committee of the Society at PP03, that the organization should reorganize and become a forum for all scientists and physicians working on purines and pyrimidines all around the world. For this (and other) reasons the ESSPPMM has been reorganized into an International Society, the Purine and Pyrimidine Society (PPS), providing a forum for all scientists working on the metabolism of purines and pyrimidines with ultimate application to medical problems. It was felt by a number of members of the ESSPPMM that the basis for membership had

become too narrow and that a more international focus should be sought. In addition, the European meetings (every two years) coincided occasionally with the International Meetings (every three years). Therefore, starting from 2007 all new meetings will be international meetings, alternating every two years between a European and a non-European country. This biennial meeting will form an excellent basis for extension of the current collaborations and to have an exchange between the various disciplines; an important aspect of current translational research. Information about the Purine and Pyrimidine Society, its meetings and its publications can be found on the web site www.ppsociety.org, and members are encouraged to contribute to the information contained on this site.

This is the second time that *Nucleosides, Nucleotides & Nucleic Acids* will publish the proceedings of the meeting [first Proceedings Vol. 23, issue 8–9, 2004]. On both occasions the quality of the publications was ensured by taking the papers through a normal review procedure. It is the intention to continue this collaboration with *NNN* in the future.