



INTERNATIONAL CONFERENCE ON LABORATORY MEDICINE

**ENZYMES:
OLD MOLECULES WITH NEW CLINICAL
APPLICATIONS**

SYMPOSIUM DEDICATED TO THE MEMORY OF PROFESSOR ANGELO BURLINA

**OCTOBER 24, 2006
AULA MAGNA DEL BO
UNIVERSITY OF PADOVA**

**OCTOBER 25, 2006
AULA MORGAGNI
UNIVERSITY HOSPITAL OF PADOVA**

Tuesday, 24 October 2006

**First Session
ENZYMES IN CARDIOVASCULAR DISEASES**

Coordinator: Martina Zaninotto

Chairmen: *F. Salvatore (Napoli, Italy)*
S. Iliceto (Padova, Italy)
P. Cappelletti (Pordenone, Italy)

**A personal history of markers
of myocyte injury**

Jack H. Ladenson

***Division of Laboratory and Genomic
Medicine and the Department of Pathology
and Immunology, Washington University
School of Medicine, St. Louis, Missouri, USA***

The measurement of proteins in blood to reflect damage to the heart is one of the most

successful applications of biomarkers to identify a major health problem. The use of a blood test to identify organ or cell injury requires a substance that is very abundant in the target cell, has a means of reaching the circulation, a reasonable half-life in blood, and ideally a specific form reflective only of the target cell or tissue. Since the major role of the myocyte is contraction, proteins involved in this function or the energy to support it should be good candidate markers. All biomarkers that have been used to detect cardiac damage conform

with this expectation, from the introduction of the aminotransferases in the 1950's to the application of the troponins in the 1990's. This history is reviewed, with emphasis on my experiences with developing assays for CK-MB and Troponin I.

Cardiac markers: state-of-the-art

Allan Jaffe

***Cardiovascular Division, Mayo Clinic,
Rochester, Minnesota, USA***

The explosion in cardiovascular biomarkers has been stimulated in large part by proteomics, genomics and an improved understanding of the pathophysiology of cardiovascular disease, and new advances are occurring rapidly. In the past few years, major changes have evolved in cardiac troponin, B-type natriuretic peptide, and C-reactive protein which will markedly impact on their clinical utility. These changes include greater sensitivity, a better understanding of what specific fragments are being measured, and how these markers may best be interpreted. The need for new markers will be emphasized. As with other scientific disciplines, the work of most current investigators has benefited from that of eminent predecessors, in recognition of which this presentation is dedicated to the late Professor Angelo Burlina.

New biochemical markers: from bench to bedside

Martina Zaninotto

***Department of Laboratory Medicine,
University Hospital, Padua, Italy***

Evaluation of patients presenting to hospital with chest pain or other signs or symptoms suggesting acute coronary syndrome (ACS) is problematic, time-consuming and sometimes expensive, even if new biochemical markers, such as troponins, have improved the ability to detect cardiac injury. However, patients with normal troponin values are not necessarily risk-free for major cardiac events. Recent investigations indicate that the overall patient risk may be assessed earlier than previously, thanks to new knowledge acquired concerning the

pathobiology of atherosclerosis and molecular events involved in the progression of disease, thus allowing the development of new biochemical markers.

The behaviour of some selected markers during the different phases of development of cardiovascular disease are outlined, focusing on: A. Present use of biomarkers in the diagnosis of patients with cardiovascular disease; B. Identification of emerging markers that provide relevant information on the inflammatory process; C. Development of biomarkers whose circulating concentrations suggest the status of plaque instability and rupture.

The overall utility of a cardiovascular biochemical marker depends not only on its biological plausibility, but also on the availability at a reasonable cost of rapid, high quality assays, and their correct interpretation by clinicians using optimal cut-offs. Therefore, the crossing from bench to bedside for each new marker requires concurrent advances in: A. Characterization of analytical features and the development of routine assays; B. Assessment of analytical performance and interpretative reporting of test results; C. Training of physicians to use the array of biomarkers available appropriately and to interpret them correctly. This approach calls for the coordinated support of clinicians, technology experts, statisticians, and industry so that new biochemical developments can be of optimal value.

Polymorphisms and gene expression of enzymes involved in cardiovascular diseases

Giuliana Fortunato

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Atherosclerosis, a multi-factorial disease, is the main determinant of cardiovascular disease (CVD) that has a high mortality and morbidity in Westernized countries. Gene polymorphisms and gene expression related to the atherosclerotic process can be identified using a genome-wide approach, or by looking for candidate disease-causing genes. Using these procedures various

genes, including paraoxonase genes, which are involved in lipid metabolism, oxidation, inflammation and coagulation, have been linked to atherosclerosis. Evaluation of these gene polymorphisms, together with traditional and novel biochemical parameters, may help identify individuals at high risk of CVD. In addition, gene expression studies can provide novel insights into the molecular mechanisms of lesion development and progression. Genetic characterization of susceptibility genes may also lead to new drugs for the prevention and treatment of atherosclerosis.

Pharmacogenomics and pharmacoproteomics for cardiovascular drugs

G rard Siest

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For the 20 classes of cardiovascular drugs, many enzymes are involved in man at the pharmacokinetic and pharmacodynamic levels.

Taking the antihypertensive drugs as examples, the variability in blood pressure response is very high in different individuals. The first to be involved in the patient response are the drug metabolizing enzymes (phases I, II and III): CYP 2D6; CYP 2C19; CYP 3A4; ABC B1 transporters. These enzymes are responsible for important side effects or drug interactions, and they explain a great part of the cardiovascular drug response variability. Genotyping of the most important CYP is today easy, but no satisfactory tools have been developed for the ABC transporters and the other phase I and phase II enzymes.

The second group of enzymes involved are linked to the pharmacodynamic action of the drugs: enzymes of the rennin-angiotensin system; enzymes of lipid metabolism. They are all polymorphic. Angiotensin-converting enzyme (ACE) is the most studied target with a relevant insertion-deletion polymorphism. Here again there are contradictory data which could be explained by ethnic differences, or by patient sample size which is often too small. In conclusion, enzymes largely contribute to cardiovascular drug response variability and are important determinants of personalized medicine.

Wednesday, 25 October 2006

Second Session

ENZYMES IN GASTROINTESTINAL DISEASES

Coordinator: Daniela Basso

Chairmen: *D. Goldberg (Toronto, Canada)*
R. Naccarato (Padova, Italy)
G. C. Guidi (Verona, Italy)

H. pylori vacuolating cytotoxin A, intracellular enzymes, and gastric inflammation

Marina de Bernard

*Venetian Institute of Molecular Medicine,
and the Department of Biology, University
of Padua, Padua, Italy*

Helicobacter pylori is a Gram-negative bacterium which infects almost half of the population worldwide and represents the major cause of gastroduodenal pathology, such as duodenal and gastric ulcer, gastric cancer, B-cell lymphoma of mucosa-associated lymphoid tissue (MALT). *H. pylori* colonization is followed by infiltration of the gastric mucosa by polymorphonuclear cells, macrophages and lymphocytes. Two of the major *H. pylori* virulence factors are the vacuolating cytotoxin (VacA) and the *Helicobacter pylori* neutrophil-activating protein (HP-NAP). VacA has been proposed as a modulator of immune cell

function because of its capacity to interfere with antigen presentation and to inhibit T cell activation. HP-NAP was designated as a neutrophil-activating protein because it stimulates high production of oxygen radicals from neutrophils. We have recently demonstrated that HP-NAP is able to recruit leukocytes *in vivo* and to stimulate either neutrophils or monocytes to release IL-12, a key cytokine for the differentiation of naïve Th cells into the Th1 phenotype. These findings indicate that both VacA and HP-NAP play a major role in generating and maintaining the gastric inflammatory response associated with *H. pylori* infection.

Non-invasive approach to the diagnosis of gastric and liver diseases

Mario Plebani

***Department of Laboratory Medicine,
University-Hospital of Padova, Italy***

In patients with both chronic liver diseases and dyspepsia there is a need for non-invasive, inexpensive and effective laboratory tests. These should not substitute but complement and integrate the information derived from invasive techniques such as liver biopsy and esophago-gastro-duodenoscopy. Natural history studies indicate that advanced fibrosis and cirrhosis develop in about 20%-40% of patients with chronic hepatitis B or C, and in a similar proportion of those with alcoholic or non-alcoholic steatohepatitis. In recent years there has been increasing interest in the possibility of identifying and assessing liver fibrosis by using non-invasive surrogate markers measurable in peripheral blood. In particular, many studies have evaluated “direct” markers of fibrogenesis, while a second approach is based on the evaluation of single or combined biochemical parameters (“indirect” markers) that reflect the stage of liver disease. Combination panels of biomarkers have been shown to improve the accuracy of the individual tests, and with the use of algorithms based on sequential combination of non-invasive biomarkers a high diagnostic accuracy has been achieved. A biochemical panel which includes the measurement of serum pepsinogens I and II, gastrin G-17 and anti-*H. pylori* antibodies, due to

its high negative predictive value in ruling out gastric disease, may be valuable in screening patients younger than 55 years in whom gastrointestinal symptoms are not definitive for diseases of the stomach or the liver.

DNA repairing enzymes, gene polymorphism and mitochondrial DNA mutations: role in gastrointestinal carcinogenesis

Daniela Basso

***Department of Laboratory Medicine,
University Hospital, Padua, Italy***

This presentation initially focuses on the main DNA repair pathways, highlighting their role in gastrointestinal carcinogenesis. The mismatch repair (MMR) system is inherently altered in patients with hereditary non-polyposis colorectal cancer, and plays a role in carcinogenesis in a subset of sporadic colorectal, gastric and esophageal cancers. Alterations in homologous recombination (HR) and non-homologous end-joining (NHEJ) also contribute to the development of pancreatic cancer. Gene polymorphisms of some X-ray cross-complementing (XRCCs) cofactor proteins involved in the base excision repair pathway have been investigated in relation to gastric, colorectal and pancreatic cancer. Yet only one polymorphism, XRCC1 Arg194Trp, appears to be involved in smoking-related cancers and in early-onset pancreatic cancer. The second part of this presentation describes the role of mitochondrial DNA (mtDNA) mutations in several tumor types, including those of the gastrointestinal tract. Although evidence in the literature indicates that mtDNA somatic mutations play a role in gastric and colorectal carcinogenesis, no firm conclusions have yet been reached regarding this issue in pancreatic cancer, although an mtDNA variant at 16519 is believed to exacerbate the outcome of pancreatic cancer patients, possibly because it is involved in altering cellular metabolism.

The role of protein kinases in pancreatic carcinogenesis

Holger Kalthoff

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Like many cancers, pancreatic carcinoma, which ranks fourth for cancer-related deaths in Germany, is characterized by the deregulation of numerous protein kinases, contributing to malignant initiation and progression, particularly by stimulating growth and invasiveness. The more than 500 kinases are grouped into at least six families according to their substrate specificity. Tyrosine kinases, which dimerize upon ligand binding leading to transphosphorylation of the monomers and the activation of signaling pathways, serve as a paradigm for oncogenic development. Constitutive activation of members of this kinase-family like EGFR or erbB2, by mutations or mostly autocrine mechanisms, is common in pancreatic cancer. But other kinases like the PKD1 (CAMK-family) which plays an important role in both apoptotic and non-apoptotic pathways, and CK1 (CK1-family) which has a strong impact on centrosome- and mitotic spindle formation, also show aberrant activity profiles in pancreatic cancer. The high prevalence of all these deregulated kinases provides good opportunities for therapeutic interventions in this usually-fatal disease.

Enzymes in feces: useful markers of chronic inflammatory bowel diseases

Imerio Angriman

Clinica Chirurgica I, Dipartimento di Scienze Chirurgiche e Gastroenterologiche, University of Padova, Italy

Ulcerative colitis and Crohn's disease are characterized by chronic intestinal inflammation. Since the precise etiology is still unknown, current therapies are aimed at reducing or eliminating inflammation. Endoscopy and histology on biopsy specimens remain the gold standard methods for detecting and quantifying

bowel inflammation. These techniques are expensive, invasive and not well tolerated by patients since the need for repeated examinations affects their quality of life. Although disease activity scores and laboratory inflammatory markers are widely used, they show unreliable relationships with endoscopy and histology. Thus, non-invasive, simple, and specific parameters are needed to detect gastrointestinal inflammation and fecal markers may meet these criteria.

Fecal markers have been investigated in inflammatory bowel disease (IBD) by many authors for diagnostic purposes, to assess disease activity and risk of complications, to predict relapse or recurrence, and to monitor the effect of therapy. Many inflammatory mediators have been detected in the feces such as leukocytes, cytokines and proteins from neutrophil activation. Some of these, particularly lactoferrin and calprotectin, have been demonstrated to be useful in these scenarios. Calprotectin and lactoferrin are remarkably stable and easy to detect in stool using ELISA, and they appear to be equally recommendable as inflammation markers in the lower gastrointestinal tract, especially in IBD patients.

Third Session ENZYMES IN NEOPLASTIC DISEASES

Chairmen: *E. P. Diamandis (Toronto, Canada)*
D. W. Chan (Baltimore, USA)
M. Gion (Venezia, Italy)

Apoptotic pathways and caspases in cancer diseases

Paolo Bernardi

Padova, Italy

No abstract received.

inhibits LE-triggered activation of MMP-9, PMN chemotaxis and chemoinvasion, PMN-triggered angiogenesis, and inflammation-triggered pulmonary fibrosis; it also represses tumor-cell expression of MMP-2, thereby restraining invasion and metastasis. Modern research supports epidemiological and historical evidence of the beneficial effects of these two plant-derived components, going a step further by shedding light on the potential mechanisms involved.

Matrix proteases, green tea, and hypericum - biomedical research catches up with folk medicine

Spiridione Garbisa

Department of Experimental Biomedical Sciences, Medical School of Padova, Italy

Some proteases involved in extracellular matrix degradation are instrumental not only in overcoming tissue barriers to allow normal extravasation of circulating blood cells, but also in facilitating pathological processes such as inflammation, angiogenesis and tumor invasion. The possibility of blocking these enzymes has led to the development of synthetic inhibitors, although clinical trials have been disappointing because of considerable side effects. However, long before enzymes were first isolated, these same pathological processes were being treated in plant-based folk remedies, and today scientists are screening them for their reputed beneficial effects. Important among these are two vegetable components with protease - inhibitor activity.

The first, (-)epigallocatechin-3-gallate from green tea, is an effective inhibitor of the gelatinases MMP-2 and MMP-9, but an even better inhibitor of leukocyte elastase (LE) activity; in vivo, it blocks inflammation, angiogenesis and tumor invasion. The second, hyperforin from *Hypericum* sp,

Kallikrein enzymes as biomarkers for cancer

Eleftherios P. Diamandis

Department of Laboratory Medicine and Pathobiology, University of Toronto, Ontario, Canada, and Department of Pathology and Laboratory Medicine, Mount Sinai Hospital, Toronto, Ontario, Canada

The human tissue kallikrein (KLK) gene family, located at chromosome 19q13.4, is the largest contiguous family of proteases in the human genome. The locus encodes all fifteen members of the family, thirteen of which have been reported as potential biomarkers for several carcinomas and other non-malignant diseases. KLKs are expressed by a wide range of tissues and implicated in a number of physiological functions, including skin desquamation, semen liquefaction, neural plasticity, and regulation of blood pressure. KLK function is regulated at various levels, including transcription, translation, and activation. The proteolytic activity of kallikreins is believed to be cascade-mediated; KLKs may cross-talk with other proteases. These cascades are highly regulated through a series of feedback loops, inhibitors, autodegradation and internal cleavage. Uncontrolled proteolysis by KLKs is implicated in a large number of

carcinomas and various non-cancerous pathological conditions. As our understanding of their regulatory and functional mechanisms continues to expand, KLKs are expected to become novel targets for therapeutics.

Standardization and quality assessment of PSA assays

Catherine M. Sturgeon

Department of Clinical Biochemistry, Royal Infirmary, Edinburgh, Scotland, UK

Achieving true commutability of immunoassay test results – i.e. reporting clinical results that are comparable independent of the laboratory that produced them - is a fundamental goal for laboratory medicine which thus far has been achieved only to a limited extent for most analytes. Prostate-specific antigen (PSA) is a clinically important analyte for which, as a consequence of a number of national and international initiatives over the last decade, considerable progress has been made towards improving method comparability. However, results from different assays are still not interchangeable, a situation that is only likely to improve once broad recommendations can be made about the most clinically relevant antibody combinations. Universal implementation of such recommendations would almost certainly improve between-method agreement substantially, provided careful attention were paid to assay design and the purity of secondary standards.

Discovery and validation of clinical proteomic biomarkers as related to enzymes

Daniel W. Chan

Department of Pathology, The Johns Hopkins Medical Institutions, Baltimore, Maryland, USA

The discovery of cancer biomarkers has become a major focus of cancer research, holding promise for early detection, diagnosis, monitoring disease recurrence and therapeutic efficacy to improve long-term survival of cancer patients. Most of the functional information concerning cancer-associated genes resides in the proteome. Cancer is a complex disease, requiring a panel of multiple biomarkers in order to achieve diagnostic efficacy. Serum/plasma is the most accessible biological material collected from patients. Therefore, serum proteomic diagnostics are very attractive in designing new tests for cancer. The advent of new proteomic technologies, such as protein chips and mass spectrometry coupled with advanced bioinformatics, has made the development of potential cancer biomarkers more feasible. However, specimen collection, handling, study design and data analysis are essential components for successful biomarker discovery and validation. Multi-center case control studies should be conducted with extensive clinical validation to minimize the impact of possible confounding variables (non-biological). Enzymes and related proteins, such as inhibitors, are promising candidates for cancer diagnostics in this new scenario.

These abstracts refer to the actual presentations made by the named speaker at the actual Conference. They have been edited by David M Goldberg. They do not necessarily reflect either the content or the authorship of the full papers based on these presentations and published in this issue of *Clinica Chimica Acta*.

INTERNATIONAL SOCIETY FOR ENZYMOLOGY (ISE)

Minutes of Board Meeting Held in Padua, Italy, Wednesday 24th October, 2006,
Commencing at 10AM.

Present: Mario Plebani (President and Chair)
Eleftherios P Diamandis (Vice-President and Treasurer)
Catherine Sturgeon (Secretary)
Daniel W Chan (Councillor)

Attending: David M Goldberg (Editor of Newsletter)

Apologies: Francesco Salvatore (Ex-President)

1. Minutes of Previous Meetings

- a) Meeting of Board, Rome, Italy, 11th October 2005
- b) General Business Meeting, Padua, Italy, 28th October 2004

These Minutes have been posted on the website of the Society (www.ISEnzymology.org) and were approved without change.

2. Business Arising From Minutes

- a) Upgrading of Website

This project, previously approved by the Board at a cost of \$CN 1,800, of which one-half has already been paid, is being undertaken by our webmaster, Mr Arun Karumanchiri, with input from Drs Goldberg and Diamandis. A Report prepared by Mr Karumanchiri was circulated, including a new design for the Home Page and a new Site Navigation Menu. Some pages, eg *Executive Board, Committees*, had been combined, and others, eg *What's New at this Web Site, What are PDF Files?* were deleted. The Board preferred the Home Page to include *About ISE* rather than *Announcements*, and expressed a desire to see the specific e-mail addresses of all office-bearers included. Current progress was considered satisfactory, and it was hoped that the further improvements in text and typography would enhance the value of the website.

- b) Links With Commercial Companies

Drs Chan and Diamandis agreed to pursue this matter once the website upgrade has been completed.

- c) Category of Associate (Junior) Members

It was agreed to take no action on this proposal.

- d) Slide Show for Exhibition at Meetings

Dr Diamandis indicated that he was not willing to pursue this matter further.

3. President's Report

a) ISE Newsletter

Dr Plebani expressed satisfaction with the dissemination of information concerning the Society by means of this publication that is posted initially on our website, and is subsequently published in *Clinica Chimica Acta*. Two issues had appeared since our last meeting. The first included the Minutes of the Board Meeting in Rome, a synoptic account of the Symposium *Standardization in Clinical Enzymology* held in Rome, and a preliminary announcement about the current Padua meeting. The second included an obituary of Dr A. R. Henderson who had earned an international reputation for his work on enzymology, together with the agendas of the Board and General Business Meetings scheduled for Padua, as well as the complete scientific program for the Symposium *Enzymes: Old Molecules With New Clinical Applications*.

Dr Goldberg appealed to the Board for material that could be used to expand the Newsletter, such as: information about Honours and Awards, either personally or involving personalities in the field of Enzymology; reports of major advances that could be compiled under the heading *What's New in Enzymology?*; a bibliography of key papers that members might find informative. There is an urgent need to use the Newsletter and our Website to create resources that would enhance their utility and thereby increase the visibility of the Society.

b) Composition of Board

Dr Plebani pointed out that as currently constituted, the Board comprised two fewer than the statutory number allowed by the Constitution: the positions of Vice-President and Treasurer were combined, and the position for a second Councillor had been left vacant. These steps had been taken to reduce Board expenses, the major liability of the Society at a time when its income was minimal. Dr Goldberg had been invited to attend Board Meetings in his role as Editor of the Newsletter, being ineligible for Board membership for a period of two years after the conclusion of his term as Ex-President. However, this had now expired, and the President proposed that Dr Goldberg be co-opted to fill the vacant position of Councillor for the remaining tenure of the present Board, a move that would involve no additional cost to the Society. This was approved.

4. Treasurer's Report

Dr Diamandis presented a brief financial report at the Padua Meeting but they ISE Board requested more details.

5. Secretary's Report

Dr Sturgeon raised the question of the Society's current active membership. Based on previous responses to postal and e-mail enquiries sent out to all 403 names listed as members in 2004, this appears to be 103, all Life Members, for whom full postal addresses are available. e-mail addresses are known for 91 of these. She will compile a list of these persons with the relevant details.

Ways of increasing the membership were discussed. Notwithstanding Item 2c above, and previous negative experience with a category of Corresponding Membership that was abandoned two years ago, it was resolved that all speakers and registrants at future

meetings of ISE for a trial period should receive an invitation from the President to join the Society either as Full Members with payment of the subscription (currently \$30 per year payable for a minimum period of two years, or Life Membership at the rate of \$300), or as Non-Voting Members. The latter will have all the privileges of membership but would not be eligible to stand for office or to vote on matters affecting the Society, and their status will be reviewed after a period of 5 years. This will take effect with the present meeting, and Dr Plebani will issue such invitations to the speakers and registrants.

6. Report on Meetings

a) Standardization in Clinical Enzymology, Rome, 12th October 2005

Dr Plebani referred to the fact that this Symposium, forming part of the official program of the 37th National Congress of the Italian Society for Biological Chemistry, had attracted a satisfactory attendance and had been organized at no cost to ISE. A report on the Symposium had been published in the Newsletter of December 24th, 2005 (see *Clinica Chimica Acta* 2006:366:S1-S3 and ISE website), and extended abstracts of all presentations had been posted on the website. The Proceedings were not published in full.

b) International Conference on Laboratory Medicine, Padua, 24th-25th October 2006

This meeting, *Enzymes: Old Molecules with New Clinical Applications*, was due to start later in the afternoon. The Full Program had been published in the Newsletter that appeared in *Clinica Chimica Acta* at the beginning of the month, and on the website several months earlier. A registration of around 150 was expected. The Board, by postal vote (e-mail), had approved an allocation of \$10,000 from ISE funds towards the cost of the meeting. A full report will appear in the Newsletter and it is hoped to publish the Abstracts of all presentations. Selected papers from this meeting will form a Special Issue of *Clinica Chimica Acta* with Dr Plebani acting as Guest Editor. He was congratulated by the Board for having put together an excellent scientific program, and for the congenial arrangements made for accommodation and associated cultural events.

c) Liaison with AACC

Dr Chan reported that he had met with Dr Donald Young to explore the possibility of a free-standing meeting in USA jointly sponsored by the Proteomics Division of AACC (of which he is Chairman) and ISE, a venture that would call for significant financial input from the Society. An alternative would be to compete for a session forming part of the official program of the AACC National Meeting. If successful, all expenses would be paid by AACC. The first such opportunity would be the meeting scheduled for Washington DC in 2008. The Board favoured the latter proposal, and Dr Chan agreed to proceed accordingly. He also undertook to post information about ISE into the Newsletter and website of the Division and to examine other potential links between the two organizations.

d) Further Links With IUBMB

Dr Goldberg reviewed the correspondence that had been circulated to the Board concerning his discussions with the organizers of the Joint IUBMB-FEBS Conference on *Biochemistry of Cell Regulation* to be held in Athens, Greece from June 28 to July 3, 2008. This had led to a proposed one-day Satellite Symposium to be held at the University of Athens campus on Friday 27th June under the title *Enzymes in Cell Regulation: Disease Implications*. Dr Andreas

Scorilas, with support from Prof Orestes Tsolas, had agreed to take care of the local administrative arrangements including liaison with IUBMB and FEBS, both being senior members of the parent organizations with responsibility for the main Conference. Dr Goldberg's original suggestion was that ISE would look after the cost of the Scientific Program, with 4 of the proposed 8 -10 speakers coming from the Board of ISE and the remainder being local experts (including Drs Scorilas and Tsolas), or drawn from scientists from other countries who were already committed to attendance at the main Conference. It was hoped that co-sponsorship might also be provided by one or more of the Greek national scientific organizations. Dr Goldberg envisaged the liability of the Society being limited to \$12,500 (including the cost of the Board speakers), with free publicity through the website and mailings of the main Conference. The on-site expenses were expected to be low, with the prospect of being easily covered by registration, and it was thought that the topic would be of great interest to those attending the Conference since, while relevant to the main theme, it did not overlap with any of the designated sessions.

A stumbling block had been the fact that, while agreeing to the proposal in general, the IUBMB-FEBS organizers seemed to require that all who attended the ISE Symposium should also register for the main Conference at a cost of >500 euros. A further proposal was submitted by Dr Scorilas and circulated at this meeting that appeared to circumvent this objection. It projected a Budget for on-site costs of 12,200 euros plus a management fee of 4,000 plus VAT, or 12% of the total revenues plus VAT. On the basis of early and late Registration Fees of 120 and 150 euros, respectively, with reductions for students, and a projected 100 registrants in each category, total income was estimated at 21,500 euros.

The Board still expressed concerns about this proposal, since ISE would still have to bear responsibility for the cost of speakers as outlined in Dr Goldberg's original outline. Before reaching a final decision, it required answers to the following questions:

1. Has IUBMB-FEBS withdrawn its insistence that all attendees must also register for the main Conference?
2. Is information available on the total number of registrants attending earlier IUBMB-FEBS conferences?
3. How many local scientists over and above those attending the main Conference can be realistically expected?

It is likely than unless satisfied that the maximum liability to ISE can be contained at the level envisaged in Dr Goldberg's original proposal, the Board will not proceed with this Symposium.

7. Other Business

Dr Diamandis spoke in favour of ISE developing a close relationship with other Societies devoted to more specialised aspects of Enzymology, such as the Kallikrein Society. This organization planned to hold an International Symposium of Kallikreins and Related Peptides in Santorini, Greece, October 16 – 18, 2007. The Board agreed that ISE will co-sponsor this meeting, and confirmed its previous agreement reached by e-mail authorising a grant of \$5,000 as its contribution.

8. Adjournment

The meeting adjourned at 13.20 hours.