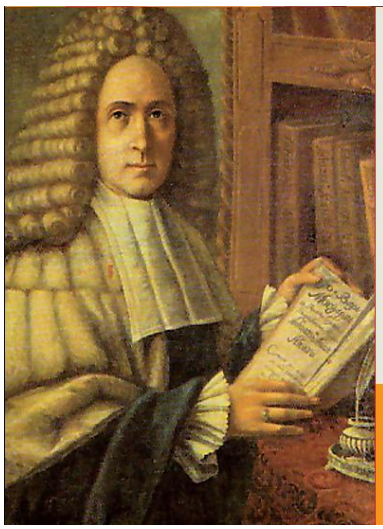

MORGAGNIAN YEAR 2011-2012
300° ANNIVERSARY OF G.B. MORGAGNI
INAUGURAL LECTURE
AT THE UNIVERSITY OF PADUA
(1712-2012)

UNIVERSITÀ DEGLI STUDI DI PADOVA

Advances in Medicine

Padua
March 23-24
2012

Aula Magna
«Galileo Galilei»
Palazzo Bo
via VIII Febbraio, 2 - Padova

ABSTRACTS

Introductory Remarks

Gaetano Thiene
University of Padua, Italy

The University of Padua celebrates Giovanni Battista Morgagni, the anatomist who started teaching in our Gymnasium 300 years ago (1712) and introduced the concept of organ pathology as the cause of signs and symptoms of the diseases. There is a general consensus that he established pathological anatomy as science, thus changing the course of medical diagnosis. With the Morgagni's method of clinical-pathologic correlations, the empiricism of anatomical observation became Medical Science and his book *"De sedibus"*, published 250 years ago (1761), represented the dawn of physiopathology. Major advances occurred in Pathology along the centuries. With the employment of the microscope Rudolph Virchow discovered the microcosme of cell pathology, Gregor Mendel established the principles of genetic heritage, Louis Pasteur and Robert Koch detected bacteria as cause of transmissible infective disease, Max Knoll and Ernst Ruska increased magnification by inventing electron microscopy, James Watson and Francis Crick discovered the DNA and genetic code, Kerry Mullis cloned the DNA by polymerase chain reaction, opening the new avenues of molecular pathology. On the clinical setting, several diagnostic testings developed parallel to the Anatomical Theatre: Radiology, Cat, Echo, CT and MR labs, besides the Surgical Theatre. The "dissection" of the human body is now feasible in vivo with a sensitivity and specificity equal to the classical postmortem investigation.

This meeting will deal with the great achievements in cell biology, diagnostic testing, therapeutics, surgery since the time of Morgagni. Is still there a room for autopsy and Morgagni' method of clinicopathologic correlations? The late Jesse E. Edwards, father of cardiovascular pathology, stated in1999: «*At this point in the history of medicine, the leaders in the field of diagnostic aids have come from a class of people familiar with the autopsy, and development of these tests and many others have been supported by anatomic observations made by pathologists and clinicians working together at the autopsy. Now, persons in the diagnostic fields are being educated and trained in a period not only of declining incidence of autopsy, but, worse than that, absence of the clinician from the few autopsies that are being performed... Unless that trend reverses itself, it is my prediction that the day will come when current and future teachers will miss the fundamental instruction on which the practice of medicine has been built*.»

March Friday 23, 2012

Oncology

Chairpersons:

Alberto Amadori,
Stefano Piccolo,
Gianpietro Semenzato
(Padua, Italy)

09.30 Antiangiogenic therapy of tumors
Napoleone Ferrara (San Francisco, USA)

10.15 Causes and consequences of microRNA disregulation in cancer
Carlo Croce (Columbus, USA)

11.00 COFFE BREAK

Anti-Angiogenic Therapy of Tumors: New Insights

Napoleone Ferrara

Genentech, Inc, 1 DNA Way, South San Francisco, CA, 94080, USA

Angiogenesis, the development of new blood vessels, is a fundamental pathophysiological process. Vascular endothelial growth factor (VEGF)-A is a key regulator of growth of blood vessels during embryonic development and in a variety of physiological processes, such as skeletal growth and reproductive functions . Anti-VEGF-A monoclonal antibodies or other VEGF inhibitors have been shown to block tumor growth and neovascularization in numerous preclinical models, consistent with an important role of VEGF-A in tumor angiogenesis. We developed a humanized anti-VEGF-A monoclonal antibody (bevacizumab) to test the hypothesis that blocking VEGF-A-induced angiogenesis may result in a clinical benefit in tumor patients. Bevacizumab has been approved by the FDA and worldwide for the treatment of several malignancies. Furthermore, blocking VEGF-A prevents vision loss and has a major impact on the progression of neovascular age-related macular degeneration and ischemic retinal disorders.

We have been recently investigating the mechanisms of refractoriness/resistance to anti-VEGF therapies in various tumor models. These studies indicate that, depending on the model, different pro-angiogenic mechanisms may be implicated. We identified factors produced by tumor-infiltrating myeloid cells or by fibroblasts[9] were identified as key mediators of VEGF-independent angiogenesis. Efforts are ongoing to determine the translational significance of such findings.

Causes and Consequences of microRNA Disregulation in Cancer

Carlo Croce

Department of Molecular Virology, Immunology and Medical Genetics

The Ohio State University Medical Center

During the past several years it has become clear that alterations in the expression of microRNA genes contribute to the pathogenesis of most, perhaps all, human malignancies. These alterations can be caused by a variety of mechanisms, including deletions, amplifications or mutations involving microRNA loci, by epigenetic silencing or by dysregulation of transcription factors targeting specific microRNAs. Since malignant cells show dependence on the dysregulated expression of microRNA genes, which in turn control or are controlled by dysregulation of multiple protein coding oncogenes or tumor suppressor genes, these small RNAs provide important opportunities for development of future microRNA based therapies.

March Friday 23, 2012

Pathology

Chairpersons:

Ambrogio Fassina,
Massimo Rugge,
Marialuisa Valente
(Padua, Italy)

11.30 Anatomic pathology: from descriptive cellular anatomy to predictive molecular pathology
Manfred Dietel (Berlin, Germany)

12.15 Pathological observation: history and procedures – Domine, ut videam
Gianni Bussolati (Turin, Italy

13.00 LUNCH

Anatomic Pathology: from Functional Anatomy to Molecular Pathology

Manfred Dietel

Institute of Pathology, Charité, Humboldt University Berlin, Germany

To define a disease as an organ related malfunction was the outstanding discovery of G.B. Morgagni (1682–1771), the famous Italian anatomist or, to be more precise, pathologist. Thanks to his groundbreaking work, Morgagni persuaded the world of what we now take for granted: the signs and symptoms of disease depend on where the anatomy is abnormal. Therefore the five books on "*De sedibus et causis morborum"* mark the starting point of anatomic pathology and beyond this of scientific medicine. One of his successors in thinking and taking action was R. Virchow (1821-1902) who developed Morgagni's concept further towards the *"Cellularpathologie"* emphasizing that the individual cell is the locus of the disease and that treatment should be directed to normalize its aberrant function. From that on the stepwise discovery of molecules and their specific functions enabled the following generations of pathologists to understand more and more the details of the complex inter- and intracellular interactions which today finds its reflexion in the field of molecular pathology.

This rapidly growing field is gaining center stage in tissue based diagnostics and clinical management of infectious diseases and tumors as well as in the pharmaceutical development of new anti-cancer drugs. To read a patient's tissue as "deeply" as possible and to obtain combined information on morphological, genetic, proteomic as well as epigenetic grounds is both challenge and chance of modern anatomic pathology.

Applications of new immunological and molecular techniques play an increasing role in the routine process of tissue-based diagnostics of infectious and neoplastic diseases as well as in translational cancer research. The major up-coming challenges are

- to directly detect a broad spectrum of microorganisms in surgical specimens,
- to precisely and reproducibly diagnose malignant tumors, even rare lesions, and to establishe internationally accepted diagnostic algorithms,
- to define the individual prognosis of the actual patient as precise as possible,
- to assess the probability of metastases, e.g. in case of clinical state M0 at time of tumor diagnosis and – of utmost importance -
- to predict response/resistance of each individual tumor against conventional or targeted anticancer drugs.

Due to continuous technical developments in immunohistochemistry (IHC) and in-situ hybrization (ISH) assisted by different molecular and computational techniques the power of diagnostic histopathology has increased dramatically during the last decade. Among others, the most impressive new innovations are

- multicolor IHC
- fluorescence and bright-field ISH
- combined IHC-ISH for double and triple stainings
- tissue adapted PCR/PCR variants and
- tissue based sequencing/mutation analyses.

These techniques all have to be performed under standard operating procedures and continuous quality control in order to guarantee reliable results to the benefit of the patients. Combined application of the different approaches will further improve the importance of histological diagnoses and their predictive accuracy.

In oncology, the application of new targeted compounds, e.g. therapeutic antibodies or kinase inhibitors, has achieved promising results in the clinics. However, the targeted drugs are efficacious only in a limited number of tumors that express the target molecules. Classical examples are Her2 / trastuzumab in breast and gastric cancer, KRAS wild type colon / panitumumab (Vectibix®) or cetuximab (Erbitux®) and EGFR-mutated non-small-cell lung cancer responsive to gefitinib (Tarceva®) and erlotinib (Iressa®). Only a few weeks ago, the BRAF-inhibitor vemurafenib (Zelboraf®) was approved in Europe for the treatment of malignant melanomas, which carry the BRAF V600 mutation. Further examples are given in tab. 1.

A very promising novel diagnostic technology is based on multi-gene analyses, which for e.g. can predict the outcome/response to chemotherapy. An example, in patients with ER+/Her2 neg. / N 1-3 breast carcinoma the 2nd generation multi-gene test EndoPredict® is able to indicate whether a patient should be treated by anti-ER drugs alone or whether an additional chemotherapy is necessary. Today the predictive accuracy for a ten-year period is 96%.

In summary, all further efforts should be directed to improve the tissue-based diagnosis and predictive relevance of surgical pathology and to provide the clinicians with all those information needed for optimal treatment.

Table 1. **Examples of predictive molecular pathology as prerequisite for the application of targeted drugs**

gene/ protein	**molecular alteration**[1]	**tumor**	**drug**	**remarks**
ER/PR	(over-)expression	breast cancer	Tamoxifen, aromatase-inhibitor	anti-hormone
HER-2	gene amplification/ overexpression	breast and gastric cancer	Trastuzumab	anti-HER2-moAB
Erb1 und Erb2	gene amplification, overexpression	breast cancer	Lapatinib	dual TKI[3]
KRAS	exclusion of mutations in codon 12/13	metastasized CRC	Cetuximab , Panitumumab	anti-EGFR-moAB
EGFR[2]	actv. Mutation in Exon 18, 19, 20 or 21	NSCLC	Gefitinib, Erlotinib	EGFR-TKI
bcr/abl	mutation	chronic myeloid leukaemia	Imatinib	BCR/ABL TKI
c-kit / CD117	exon 9 mut / overexpression	gastrointestinal stromal tumor	Imatinib	BCR/ABL TKI
CD20	overexpression	B-cell non-Hodgkin lymphoma	Rituximab	anti-CD20-moAB
BRAF	mutation in codon V600E, V600 R, V600 K	malignant melanoma	Vemurafenib	Serin/Threonin (BRAF)-Inhibitor
EML4-ALK	mutation/inversion / overexpression	NSCLC	Crizotinib	RTKI[4]
8 Gene	pattern of genetic alterations, e.g.. EndoPredict-Assay	ER + / HER2 - Mammakarzinom	TAM +/- chemotherapy	Multi-gene test / 2. Generation

[1] in FFPE tissue, [2]epidermal growth factor receptor, [3]tyrosine kinase inhibitor, [4]receptor tyrosine kinase inhibitor

Pathological Observation: History and Procedures – *Domine, ut videam*

Gianni Bussolati
University of Turin, Italy

The study of Pathological lesions, of their varieties and evolution, is based on visual appreciation. This process has to go through the distorting gap of technical processes, apparatuses and procedures permitting us to understand (or to "grasp") what we look at. In fact, "to see" means to look and, in parallel, to interpret, thus activating mental processes which do determine the progress of science. Galileo's telescope itself would not (and historically did not) allow by itself a scientific progress. It was the dialectic inter-change of "sensata esperienza" and "certa dimostrazione"(in Galileo'words), of "sense experience" and "sure demonstration" which determined the discovery. We are presently celebrating Morgagni's scientific breakthrough which opened the way to the understanding of the nature and cause of diseases, hence today's progresses in cure and prevention, but even Morgagni had to devise or exploit a novel procedure, that of "looking inside". His successors, in the 19th Century, being obsessed by the need to preserve tissues and organs so as to be able to show, teach and analyse pathological lesion, had to devise a variety of techniques. Museums of Pathological Anatomy started to be established in different European countries, and especially in Northern Italy new techniques, making use of available chemical reagents, were experimented in order to preserve tissues. It was soon realised that tissues had to be fixed, and fixation, mainly with mercuric chloride, was followed by desiccation. The quality and value of these preparations can still be admired in Museums of Pathological Anatomy at the Universities of Torino, Parma, Bologna and Firenze. These preparations testify the prevailing diseases at that time: syphilis, tuberculosis, malformations.. These techniques of organ/tissue preservation were brought to perfection by Lodovico Brunetti in Padoa. He experimented and finally standardized "tannization" as the method of choice. The discovery, at the end of the 19th Century of Formaldehyde, associated with perfectioning of the paraffin-embedding procedure, established by Beck in the same period, were the technical breakthrough which permitted standardization of histopathological techniques and the flourishing of Surgical Pathology as the diagnostic discipline which we are still practicing today. Later on, a further step forward was permitted by the serendipitous observation that a simple treatment with heating was able to restore the antigenic properties in Formalin-fixed Paraffin-embedded tissue sections. This prompted the widespread application of immunohistochemical techniques to routine diagnosis and a very extensive development of novel classifications of human diseases on the base of iimmunophenotypic features. As a result, the goal of histopathology was not anymore the description of morphologic features alone, but the discipline evolved as an integrated medical discipline, with heavy impact on surgical intervention and medical treatment. This scenario demanded, in return, a proper standardization of fixation and embedding procedures, since the goal was not anymore morphological (structural) perfection, but a proper antigenic preservation as well. The future is represented by the link of structural and functional parameters, and by a proper analysis of the genetic properties of different cell types. Taking advantage of the great progresses of genetic characterization of tumors, it is now possible to further exploit our tissue sections and to derive information of great medical impact. Morgagni's lesson of the use of autopsies for understanding human diseases and thus helping patients is still valid and alive. We have to follow the spirit of his mandate, and to look forward using both old and novel procedures.

March Friday 23, 2012

Neurosciences

Chairpersons:

Corrado Angelini,
Tullio Pozzan,
Carlo Reggiani
(Padua, Italy)

14.15 Mirror neurons

Giacomo Rizzolatti (Parma, Italy)

15.00 The placebo effect: how the ritual of the therapeutic act changes the patient's brain

Fabrizio Benedetti (Turin, Italy)

15.45 COFFE BREAK

The Mirror Mechanism: Theoretical Bases and Clinical Relevance

Giacomo Rizzolatti
Dipartimento di Neuroscienze, Università di Parma

"A mere visual perception, without involvement of the motor system would only provide a description of the visible aspects of the movements of the agent, but it would not give precise information about the intrinsic components of the observed action which are critical for understanding what the action is about, what is its goal, and how to reproduce it". This sentence by Marc Jeannerod beautifully describes the importance of motor system in action perception. In my talk I will elaborate on this theme describing a mechanism- the *mirror mechanism*- that allows one to understand the others "from the inside".

In the first part of my lecture, I will review the basic functional properties of frontal and parietal mirror neurons. I will describe first their *motor* properties. I will show that, as most neurons in the premotor cortex, mirror neurons code the goal of a motor act. I will review then their *visual* properties showing that mirror neurons represent a mechanism that allows a direct understanding of *what* the agent is doing.

I will discuss then the mirror mechanism in humans showing that in humans this mechanism is also involved in imitation. I will show then that, although there are several mechanisms through which one can understand the behaviour of others, the mirror mechanism is the only mechanism that allows understanding actions and emotions of others from the inside, giving the observing individual a "first-person" person grasp of other individuals' behavior.

In the last part of my talk, I will discuss the clinical relevance of the discovery of the mirror mechanism. I will show that while children with autism understand the *what* of an observed motor act, they have impairments in recognizing the *why* of it as well as the *how (*vitality form*)* the actions of others are accomplished. I will conclude presenting some data on mirror mechanism-based rehabilitation following cerebral stroke.

The Placebo Effect: How the Ritual of the Therapeutic Act Changes the Patient's Brain

Fabrizio Benedetti

Department of Neuroscience, University of Turin Medical School,
and National Institute of Neuroscience, Turin, Italy

Although placebos have long been considered a nuisance in clinical research, today they represent an active and productive field of research and, due to the involvement of many mechanisms, the study of the placebo effect can actually be viewed as a melting pot of concepts and ideas for neuroscience. Indeed, there exist not a single placebo effect, but many, with different mechanisms and in different systems, medical conditions and therapeutic interventions. For example, brain mechanisms of expectation, anxiety and reward are all involved, as well as a variety of learning phenomena, such as Pavlovian conditioning, cognitive and social learning. There is also some experimental evidence of different genetic variants in placebo responsiveness. The most productive models to better understand the neurobiology of the placebo effect are pain and Parkinson's disease. In these medical conditions, the neural networks that are involved have been identified: that is, an opioid-cannabinoid-cholecystokin-dopamine modulatory network in pain and part of the basal ganglia circuitry in Parkinson's disease.

The nocebo effect is a phenomenon that is opposite to the placebo effect, whereby expectation of a negative outcome may lead to the worsening of a symptom. As for the placebo counterpart, the study of pain has been fruitful in recent years to understand both the neuroanatomical and the neurochemical bases of the nocebo effect. Recent experimental evidence indicates that negative verbal suggestions induce anticipatory anxiety about the impending pain increase, and this verbally-induced anxiety triggers the activation of cholecystokinin (CCK) which, in turn, facilitates pain transmission. CCK-antagonists have been found to block this anxiety-induced hyperalgesia, thus opening up the possibility of new therapeutic strategies whenever pain has an important anxiety component. The reward neuronal network has been found to be involved in the nocebo effect as well. In fact, whereas the placebo response is associated to the activation of dopamine and opioids in the nucleus accumbens, the nocebo response is associated to a de-activation of both dopamine and opioids. All these findings may help understand some of the mechanisms of anxiety.

March Friday 23, 2012

Cardiovascular Sciences

Chairpersons:

Sabino Iliceto,
Mario Plebani,
Paolo Prandoni
(Padua, Italy)

16.15 The genetics of AV block
Connie R. Bezzina (Amsterdam, NL)

17.00 Management of venous thromboembolism
Harry R. Buller (Amsterdam, NL)

17.45 Concert by Galileian School

18.30 ADJOURN

The Genetics of Atrio-Ventricular Block

Connie R. Bezzina

Heart Failure Research Center, Department of Clinical and Experimental Cardiology, Academic Medical Center, Amsterdam, The Netherlands

Rhythmic and synchronized contraction of the atria and ventricles crucially relies on the proper generation and conduction of the cardiac electrical impulse, which leads to a coordinated mechanical response in cardiomyocytes through excitation–contraction coupling. The cardiac electrical impulse originates in the sinus node and subsequently activates the atria which propagate it to the atrioventricular node. Conduction of the electrical impulse through the atrioventricular node occurs slowly, allowing the atria to pump blood into the ventricles while the latter are diastolic. Subsequently, the impulse is propagated through the fast-conducting atrioventricular bundle, the bundle branches, and, ultimately, the Purkinje fibre network, from where it reaches the ventricular working myocardium, allowing for contraction from apex to base. Atrio-ventricular conduction disease (block) describes the impairment of this electrical continuity between the atria and the ventricles and is characterized by prolongation of the PR-interval on the surface electrocardiogram (ECG). Atrio-ventricular conduction disease may be caused by mutations in a variety of genes. The disease is often progressive and involves various sites in the conduction system. Our group has identified loss-of-function mutations in the *SCN5A* gene, encoding the major sodium channel in heart, as a cause of isolated cardiac conduction disease. My presentation shall focus on *SCN5A* gene mutations as a cause of atrio-ventricular conduction disease. Furthermore, novel data obtained through genetic studies in humans and mice, identifying new genes and mechanisms impacting on atrio-ventricular conduction will be presented.

Management of Venous Thromboembolism
- the Padova Legacy -

Harry R. Buller

Dept. of Vascular Medicine, Academic Medical Center, Amsterdam, The Netherlands

Venous tromboembolism, i.e. deep vein thrombosis of the leg or arm and pulmonary embolism, is the third most common cardiovascular disease after myocardial infarction and stroke. Per 1000 inhabitants each year 2-3 individuals will develop symptomatic venous thromboembolism. As for every disease five distinct areas can be distinguished:

a) how to diagnose the disease (diagnosis)
b) why did the disease occur (etiology)
c) what is the best way to treat it (treatment)
d) how can it be prevented (prevention) and finally
e) what may happen subsequently (prognosis)

For venous thromboembolism, major progress has been made in each of these five areas in the last 25 years.

The University of Padova, in particular the department of Prof. P. Prandoni, has made numerous significant contributions to this progress.

In the presentation, the situation in 1987 for each of these areas will be described. The work performed is Padova in the last 25 years will be highlighted. Collectively, the Padova work, here described as the Padova Legacy, to the progress in this disease will be made clear.

It will conclude how the situation is in 2012.

March Saturday 24, 2012

Endocrinology and Signaling

Chairpersons:

Annalisa Angelini,
Franco Mantero,
Lorenzo Pinna
(Padua, Italy)

09.30 PI 3-kinase, metabolism and disease
Lewis C. Cantley (Boston, USA)

10.15 Endocrine hypertension: then and now
William F. Young (Rochester, USA)

11.00 COFFE BREAK

PI 3-kinase Metabolism and Disease

Lewis C. Cantley

Beth Israel Deaconess Medical Center and Harvard Medical School, Boston MA 02115

Phosphoinositide 3-Kinase (PI3K) is a central enzyme in a signaling pathway that mediates cellular responses to growth factors. This enzyme phosphorylates the 3 position of phosphatidylinositol-4,5-bisphosphate to produce phosphatidylinositol-3,4,5-trisphosphate (PIP_3) at the plasma membrane. A number of signaling proteins, including the Ser/Thr protein kinases, AKT and PDK1, contain pleckstrin homology domains that bind specifically to PIP_3. Thus, the generation of PIP_3 at the plasma membrane in response to activation of PI3K by growth factors results in the initiation of downstream Ser/Thr phosphorylation cascades that control a variety of cellular responses. The signaling pathway downstream of PI3K is highly conserved from worms and flies to humans and genetic analysis of the pathway has revealed a conserved role in regulating glucose metabolism and cell growth. Based on deletion of genes encoding the catalytic or regulatory subunits of PI3K in the mouse, PI3K mediates insulin dependent regulation of glucose metabolism, and defects in activation of this pathway result in insulin resistance. In contrast, mutational events that lead to hyperactivation of the PI3K pathway result in cancers. Activating mutations in PIK3CA, encoding the p110alpha catalytic subunit of PI3K or inactivating mutations in PTEN, a phosphoinositide 3-phosphatases that reverses the effects of PI3K, are among the most common events in solid tumors. We have generated mouse models in which a mutated form of the PIK3CA gene is expressed in a tissue specific and reversibly inducible manner. These mice develop cancers that are dependent on continuous expression of the mutant PIK3CA gene. The PIK3CA driven tumors are FDG-PET positive and turning off PI 3-Kinase with PI3K inhibitors that are in human clinical trials results in an acute decline in FDG-PET signal that precedes tumor shrinkage. These results suggest that the ability of PI3K to stimulate high rates of glucose uptake and metabolism may be critical for the survival of PIK3CA mutant tumors. The role of PI3K inhibitors for treating cancers in mouse models and in human trials will be discussed.

Endocrine hypertension: then and now

William F. Young

Chair, Division of Endocrinology, Diabetes, Metabolism, Nutrition, Mayo Clinic, Rochester, Minnesota, USA

The evaluation and treatment of pheochromocytoma and primary aldosteronism have evolved dramatically since these 2 types of endocrine hypertension were first detected and successfully treated in 1926 and 1954, respectively. Herein, the challenges that surrounded the management of these prismatic cases and the advances that have occurred since the initial descriptions are reviewed.

In 2012, approximately half of patients with pheochromocytoma are asymptomatic because their neoplasms are discovered in the presymptomatic state—because of either detection with abdominal imaging done for other reasons (eg, adrenal incidentalomas) or genetic testing in at-risk family members. In symptomatic patients with catecholamine-secreting tumors, biochemical testing with measurement of 24-hour urinary fractionated metanephrines and catecholamines and plasma fractionated metanephrines with the liquid chromatography/tandem mass spectrometry method is accurate and reliable. However, all pheochromocytomas and paragangliomas have a presymptomatic and prebiochemical phase. Thus, all biochemical testing may be normal in the asymptomatic patient with an adrenal incidentaloma and, in this clinical setting, the imaging phenotype should guide management. In symptomatic patients, catecholamine-secreting tumors have an average diameter of 4.5 cm and are usually easily localized by imaging the abdomen and pelvis with CT or MRI. Catecholamine-secreting paragangliomas are found where there is chromaffin tissue: along the para-aortic sympathetic chain, within the organs of Zuckerkandl (at the origin of the inferior mesenteric artery), in the wall of the urinary bladder, and along the sympathetic chain in the neck or mediastinum. Thus, computed imaging of the skull base, neck, and chest are indicated in selected cases. Iodine 123 MIBG scintigraphy should be considered in the following situations: (a) when the abdominal and pelvic computed imaging do not reveal the neoplasm in biochemically confirmed cases; (b) in the patient with an image-confirmed paraganglioma to detect additional paragangliomas or metastatic disease; or (c) in the patient with adrenal pheochromocytoma with suspected malignant disease (eg, tumor diameter >10 cm). Positron emission tomography is indicated in the evaluation and monitoring of patients with known metastatic paraganglioma or pheochromocytoma.

The diagnosis of primary aldosteronism is usually made in patients who are in the third to sixth decades of life. Few symptoms are specific to the syndrome and there are no specific physical findings. The degree of hypertension is usually moderate to severe and may be resistant to those pharmacologic treatments that do not block mineralocorticoid effects. Hypokalemia is frequently absent; thus, all patients with hypertension are candidates for this disorder. Several studies have shown that patients with primary aldosteronism are at higher risk than other patients with hypertension for target-organ damage of the heart and kidney. Patients with hypertension and hypokalemia (regardless of presumed cause), treatment-resistant hypertension (3 antihypertensive drugs and poor control), severe hypertension (≥160 mm Hg systolic or ≥100 mm Hg diastolic), hypertension and an incidental adrenal mass, or onset of hypertension at a young age should undergo case-detection testing for primary aldosteronism. Case-detection testing is performed with morning venipuncture for the

measurement of plasma aldosterone concentration and plasma renin activity. Confirmatory testing should be performed with 1 of the 4 accepted aldosterone suppression tests. The third management step guides the therapeutic approach by distinguishing unilateral adrenal disease (eg, aldosterone-producing adenoma [APA]) from bilateral adrenal disease (eg, idiopathic hyperaldosteronism [IHA]). Adrenal CT is performed in all patients to exclude adrenocortical carcinoma and to identify adrenal morphologic characteristics. However, in patients who want to pursue the surgical option, adrenal venous sampling is a key test. IHA and glucocorticoid remediable aldosteronism should be treated medically. In addition, patients with APA may be treated medically if the medical treatment includes mineralocorticoid receptor blockade with either spironolactone or eplerenone.

The evolution in the diagnosis and treatment of pheochromocytoma has progressed remarkably over the 86 years since the first patients were surgically cured in 1926. The diagnostic and therapeutic timeline continues. Over the next 10 years, we hope to identify more genetic causes, develop biochemical markers for "preclinical" pheochromocytoma, identify better markers for malignant disease, and develop more effective treatment options for malignant pheochromocytoma. Equally impressive has been the evolution in the diagnosis and treatment of primary aldosteronism over the 58 years since the first patient was surgically cured in 1954. Over the next decade, we hope to determine the pathophysiology of bilateral IHA, develop less invasive and less technically demanding tests to distinguish between APA and IHA, determine where low renin hypertension stops and primary aldosteronism starts, and determine the impact of genetic and environmental factors on aldosterone secretion in patients with and without primary aldosteronism.

March Saturday 24, 2012

Surgery and Transplantation

Chairpersons:

Donato Nitti,
Federico Rea,
Paolo Rigotti
(Padua, Italy)

11.30 Advanced colo-rectal cancer: how multimodality management has transformed the prognosis
Bernard Nordlinger (Boulogne, France)

12.15 Organ regeneration
Doris A. Taylor (Houston, USA)

13.00 END OF SCIENTIFIC SESSION

The Multimodality Management of Advanced Colorectal Cancer

Bernard Nordlinger
Department of Oncology and Surgery, Ambroise Paré Hospital, Boulogne, France

Colorectal cancer (CRC) is one of the most common cancers and often carries a poor prognosis. An estimated one million people are diagnosed yearly with CRC worldwide. More than half of those diagnosed with CRC are expected to develop metastatic CRC (mCRC), with the first metastases frequently appearing in the liver.

Major progress have been made in recent year in the multidisciplinary management of mCRC. They concern better and safer surgical procedures and more effective and better-tolerated chemotherapy regimens. Treatment aims and methods are being dictated by the potential resectability of liver metastases. In general, patients with liver metastases are divided into three groups: patients with resectable metastases; patients with borderline resectable metastases; and those with non-resectable metastases. For patients with advanced mCRC who are eligible for surgical resection, the aim of treatment is to remove all macroscopic disease. Surgical resection of colorectal liver metastases (CLMs) is potentially curative, with 35–45% of patients who have undergone resection surviving for 5 years after diagnosis, compared with less than 5% of unresected patients].

In resectable patients, peri-operative chemotherapy has been found to confer a disease-free survival benefit over surgery alone in patients with initially resectable CLMs

Historically, patients with numerous metastases, or extrahepatic disease or have been considered to be unresectable, but more recent studies have gradually broadened the concept of resectability . Some metastases can become resectable after shrinkage due to chemotherapy. Administration of standard cytotoxic regimens such as 5-fluoropyrimidine, leucovorin and irinotecan (FOLFIRI) or oxaliplatin (FOLFOX) in patients with initially unresectable CLMs increases the likelihood of patients undergoing secondary liver resection with curative intent

The combination of surgical resection, chemotherapy and biological agents may also contribute to an improved prognosis of patients with an aim for cure for mCRC. In addition to chemotherapy, biological agents such as the vascular endothelial growth factor (VEGF) monoclonal antibody (mAb) bevacizumab, and epidermal growth factor receptor (EGFR) mAbs cetuximab and panitumumab are becoming a component of the care for mCRC . Although significant improvement in the control of cancer was shown in large trials, the magnitude of such benefits was less than expected.

In general, the prognosis of metastatic colorectal cancer improves step by step. Multidisciplinary discussion is the basis of such progress. However it is still too early to say that metastatic colorectal cancer has become a chronic disease such as diabetes for instance.

Organ regeneration: Moving from Idea to Reality

Doris A. Taylor
Texas Heart Institute, Houston-TX, USA

Cell based organ repair and regeneration remains a lofty goal in 2012, but is no longer unimaginable. Stem and progenitor cells have been utilized for almost 15 years in patients with CVD – with mixed results – yet approval of the first products may occur soon. However, in patients with end organ damage or congenital defects cell therapy is unlikely to ever suffice.

Understanding the limitations of the existing studies, the implications of ongoing studies, and the potential of new approaches that move beyond simple cell based therapies toward actual replacement of whole tissues or organs is the aim of this presentation.

I will review the advances in stem cell biology and in scaffolds that suggest within 10 years transplantation of autologous cardiac tissues derived from an individual's stem cells or even whole heart built in the laboratory may occur.

Literature cited

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