Profiles in Cardiology

This section edited by J. Willis Hurst, M.D., and W. Bruce Fye, M.D., M.A.

Attilio Maseri

C. RICHARD CONTI, M.D., M.A.C.C.

Division of Cardiology, University of Florida, Gainesville, Florida, USA

Attilio Maseri (Fig. 1) was born in Udine, Italy, on November 12, 1935. He graduated from Padua University Medical School with full honors in 1960 and passed the postgraduate boards in both cardiology and nuclear medicine, again with full honors, at Pisa University Medical School in 1963 and 1968, respectively.

Attilio Maseri married Francesca Florio on July 31, 1960. The world of cardiovascular medicine knows what Professor Maseri has contributed to our knowledge of ischemic heart disease. His friends also know the role that Francesca played in those contributions. The following quote makes that point, "It is to Francesca, my wonderful supportive wife, that I owe the serenity of my every day life. . . Whenever in doubt about major decisions I have been able to count on her good sense; when depressed I could always count on her encouragement. She has been my *musa inspiratrice*."¹ Rarely was Professor Maseri seen anywhere in the world without Francesca.

His major contributions to research are in the field of ischemic heart disease and followed a coherent series of themes suggested by personal clinical observations: initially methodology for the study of the coronary circulation, then pathophysiology of myocardial ischemia, role and mechanisms of coronary spasm and vasoconstriction, significance of painless ischemia and mechanisms of ischemic cardiac pain, anti-ischemic therapy, and finally role and mechanisms of inflammation in acute coronary syndromes.

The Early Years

The early part of Professor Maseri's career was spent at the University of Pisa before moving to Columbia University, New York, in 1965 where he was a public health service research fellow working with Drs. Andre Cournand and H. M. Frits. In 1966, he moved to Johns Hopkins University where he was a National Institutes of Health research fellow working with Dr. Kenneth L. Zierler, Richard Riley, and Solbert Permutt. He returned to Italy in 1967 upon his appointment as assistant professor in the department of medicine and head of the coronary research group at the University of Pisa. During that time, he pioneered the development of methods for assessing regional myocardial blood flow in humans using radioactive tracers. He was the first to propose and use the 3-hour redistribution of thallium as a proof of reversibility of myocardial perfusion defects.

Coronary artery spasm was popularized by a series of systematic studies with his group in Pisa. He proved the role of coronary artery spasm in variant angina and developed a concept of "primary angina" as opposed to angina secondary to increased myocardial oxygen demand. I was fortunate to be present at the meeting in Pisa in 1976, in which the term "primary angina" evolved.² Many at that meeting began calling it "Pisa Angina." The topics discussed were at the cutting edge of ischemic heart disease by the recognized experts in the field, including Donald Gregg and Richard Gorlin. These studies in Pisa contributed significantly to the opening of new avenues of research on coronary vasomotion and, more broadly, on reduced blood supply, a common cause of angina. In the area of acute myocardial infarction and unstable angina, he observed that coronary artery occlusion in the very early phases of infarction and unstable angina was a dynamic phenomenon and results from a variable combination of coronary thrombosis, thrombolysis, and vasoconstriction.

Working in the area of silent myocardial ischemia, Dr. Maseri and his group in Pisa showed that signs of acute ventricular failure and potential fatal arrhythmias were equally frequent in painful and painless ischemic episodes, and that painful and painless ischemic episodes were equally dramatically reduced by calcium antagonists and nitrates.

Address for reprints:

C. Richard Conti, M.D.
Professor of Medicine
Division of Cardiology
University of Florida, Box 100277
Gainesville, FL 32610, USA
e-mail: conticr@medicine.ufl.edu

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FIG. 1 Attilio Maseri, M.D.

With his group in Pisa, he was the first to prove convincingly in double crossover studies that nitrates have a dramatic beneficial effect in preventing coronary artery spasm. These studies actually represented the first basis for the subsequent widespread use of coronary vasodilators as anti-ischemic drugs.

The Middle Years

In 1979, Attilio Maseri became the Sir John McMichael Professor of Cardiovascular Medicine at the Royal Postgraduate Medical School (University of London) and Director of Cardiology at the Hammersmith Hospital.

With the Medical Research Council group at the Hammersmith in London, he developed methods for measuring myocardial perfusion and metabolism by positron emission tomography. He also demonstrated that spasm as it occurs in the variant form of angina is not caused by any specific receptor agonist interaction, but by a local postreceptor smooth muscle hyper-reactivity to a variety of constrictor stimuli acting on different receptors.

With his colleagues in London, he showed for the first time that, in patients with chronic stable angina, the ischemic threshold at which attacks occur is variable. Subsequently, he demonstrated that the modulation of the residual coronary stenosis by vasomotor tone responsible for this variability was different from that observed in variant angina and that such modulation can occur in small distal coronary vessels. He also showed that a variety of neuropeptides may contribute to such modulation, and that distal coronary vessel constriction may also explain the persistence of reduced coronary flow reserve after successful angioplasty.

Maseri and colleagues made the observation that a combination of powerful constrictor stimuli and/or enhanced constrictor responses of proximal and distal coronary vessels and thrombosis are jointly responsible for ischemic attacks in patients with either acute myocardial infarction or unstable angina.

In the area of painless ischemia and mechanisms of ischemic cardiac pain, he demonstrated with the group in London that the absence of pain could not be explained only by a shorter duration or lesser severity of ischemia, by dilatation of the left ventricle, or by a generalized reduction in pain perception, and that adenosine was a major chemical mediator of ischemic cardiac pain. They hypothesized that the gating system at the level of the dorsal horn of the spinal cord is likely to play a major role in determining the presence or absence of ischemic cardiac pain.

The Later Years

Professor Maseri returned to Italy in 1991 upon his appointment as Professor of Cardiology at the Catholic University of Rome, and Director of the Institute of Cardiology at Policlinico "Agostino Gemelli."

With the group in Rome, he showed that patients with angina and normal coronary angiograms, who often present with episodes of ischemic ST-segment depression unrelated to heart rate increase with and without their usual chest pain, have an increased dispersion of regional myocardial blood flow compared with controls in the absence of detectable regional ventricular contraction abnormalities at echocardiography. They also have a paradoxical response to sublingual nitrates during exercise stress testing with worsening of ischemic signs and a marked depression of myocardial catecholamine reuptake. He proposed the hypothesis of a patchily distributed coronary microvascular dysfunction that may be caused by different mechanisms, capable of causing small focal areas of myocardial ischemia not sufficiently extensive to result in contraction abnormalities. He recently supported this hypothesis by the detection of lipoperoxidation products in the coronary sinus following pacing-induced angina in patients with syndrome X, which was of a comparable magnitude to that observed following acute coronary occlusion during coronary angioplasty. He also showed that these patients have a generalized enhanced pain perception in response to direct electrical stimulation of the heart. Thus, in such patients, angina results from a combination of focal release of adenosine and other algogenic substances distal to constricted prearteriolar coronary vessels and of an enhanced pain perception. In the area of acute myocardial infarction, he showed that a coronary vasospastic response, soon after acute infarction, is about three-fold more common among Japanese than among Caucasian patients.

With the group in Rome, he made fundamental contributions toward the identification of pathogenic roles of inflammation in unstable angina contributing to precipitation of infarction and recurrence of instability. This inflammatory component was shown to be related to any enhancement of the

individual inflammatory response rather than to specific infectious or inflammatory agents which may persist over 6 months post discharge and is detectable in immunoglobulins, lymphocytes, and monocytes.

He and his group in Rome also made the observation that an inflammatory response is observed in nearly all patients in whom infarction was preceded by unstable angina. In contrast, less than 50% of cases of totally unheralded infarction exhibit evidence of inflammation suggesting a multiplicity of pathogenic mechanisms which may require specific individual therapeutic and preventive strategies rather than a “blanket” antibiotic or inflammatory treatment.

Awards and Honors

Professor Maseri has received numerous awards and is an honorary member of numerous societies of cardiology. Among these honors are the James B. Herrick Award of American Heart Association Council in Clinical Cardiology, Lifetime membership of the Johns Hopkins Society of Scholars, the King Faisal International Prize in Medicine, and the Distinguished Scientist Award of the American College of Cardiology. Some of the distinguished lectures he has given include the Louis F. Bishop Lecture at the American College of Cardiology, the Lilly Lecture at the Royal College of Physicians in Edinburgh, the Laurence H. Green Lecture at the Brigham and Women’s Hospital in Boston, and the Denolin Lecture during the European Society of Cardiology Congress in Barcelona. Professor Maseri received the Gold Medal from the European Society of Cardiology at the annual congress in Berlin in 2002.

Summary

Professor Attilio Maseri is a clinical investigator with a remarkable track record of innovative research who, by changing traditional paradigms, contributed to shape new diagnostic techniques in pathophysiologic thinking. His research has been characterized by challenging the generalizations of ac-

cepted “wisdom” which did not offer satisfactory explanations for the observations he made in his clinical practice. The results of his clinical investigations have contributed greatly to the opening of new avenues of research and patient management in the field of ischemic heart disease. His clinical and research experiences are catalogued in 740 pages of his single-authored textbook *Ischemic Heart Disease. A Rational Basis for Clinical Practice and Clinical Research*. This book chronicles Maseri’s novel unifying vision of ischemic heart disease.

In 2001, Professor Maseri left Catholic University in Rome to take on bigger challenges in Milan where he is now functioning as Professor of Cardiology at the University Vita-Salute San Raffaele and Director of the Cardio-Thoracic and Vascular Department of the San Raffaele Scientific Institute. His research interests include application of molecular biology, differential gene expression profiling, and clinical cardiovascular research such as molecular mechanisms of coronary instability and molecular mechanisms of negative and positive ventricular remodeling.

Professor Attilio Maseri will be remembered as a thoughtful clinician, a mentor for many whose academic careers have blossomed, and a careful clinical investigator whose innovative research in ischemic heart disease will set the highest standards for those who follow in his giant footsteps.

On a personal note, I first met Attilio Maseri, his wife Francesca, and their son Filippo at the 1976 Pisa conference. What transpired at that conference influenced my own career and stimulated my continued interest in ischemic heart disease as well as my enthusiasm for the international aspects of cardiovascular medicine. I consider myself fortunate to be a friend of Attilio Maseri and to have benefited from my associations with him, both professionally and personally.

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