In the middle of April, when a storm of cherry blossoms started to fall and many cherry petals were scattered across the path in Kyoto, I was notified by his step-daughter that Dr. John Ross Jr, a legendary figure in cardiovascular medicine, had passed away on April 11, 2019 at his home in La Jolla, California, 2 years after the passing of his beloved wife Lola.

Dr. Ross devoted his life to ask the question raised by physiologists since William Harvey’s discovery of the pumping action of the heart: what are the events that constitute a normal contraction and how are these events controlled so that the normal heart can almost instantly adjust its performance to meet the rapidly varying requirement of the peripheral tissues; as well as the question raised by clinicians about how are these events disturbed when the heart fails.

Dr. Ross was not only versed in his specialty but very widely educated. He was born in New York city and it was from his mother, Ms. Jane Moulder, that Dr. Ross acquired his cultural appreciation. When I first visited his house, the sight of his living room amazed me with the woodcut prints of Utamaro and Kuniyoshi on the wall on one side and a Noh mask on the other side. Sometimes he played Chopin on the piano in his living room.

Four years prior, I received from Dr. Ross his newly published autobiography entitled “Odyssey of a Physician-Scientist” in which he described that in the early 1920s, his father Dr. John Ross Sr moved to New York city where he became an established specialist in otorhinolaryngology. As a boy, Dr. Ross often accompanied his father to the office and he described his decision to become a doctor “primarily grew out of my experiences with my father and also my mother’s statements to her friends that ‘Johnny wants to be a doctor’.”

After receiving his MD from Cornell University, he started postgraduate training in surgery at Johns Hopkins University Hospital in 1956. There, Dr. Ross made the first critical encounter of his career: Dr. Alfred Blalock, who at that time was experimenting with his landmark procedure, the Blalock-Taussig shunt, which turned blue babies back to pink. Dr. Taussig offered him a research position in surgery at the National Heart Institute (NHI) of the National Institutes of Health (NIH), Bethesda, Maryland. One day in the cardiac catheterization laboratory at the NHI of NIH, Dr. Ross performed right heart catheterization in a patient with ASD by inserting the catheter through a vein in the leg and passing it across the atrial septum and left ventricle, musing whether it might be possible to reach the left side of the heart when the atrial septum is intact. Subsequently, he began his first personal research project. He fabricated a long needle that was curved at the distal end with the proximal end. After repeating animal experiments this procedure was applied in patients in collaboration with Drs. Andrew Morrow and Eugene Braunwald. The first patient was a young man with severe mitral regurgitation because of valvular scarring from rheumatic fever in 1958. A second series of 130 patients was published in 1960, in which left atrial and left ventricular (LV) pressures were measured in many patients using the transseptal catheter with no complications. Application of the transseptal method in the pediatric age group was also confirmed. However, with increasing use of selective coronary arteriography, so-called retrograde catheterization of the left ventricle largely replaced the transseptal method. However, in 1984, transseptal left ventricular catheterization reemerged as a useful tool for treating mitral stenosis. In 1980, Dr. Inoue, who was a member of the Department of Cardiology at Kyoto University, which I used to chair, invented a catheter-tip balloon device that, when positioned in the mitral valve using the transseptal method, could be inflated to open the narrowed valve. This procedure has been used as an effective way of avoiding open-heart surgery. The transseptal method is now also widely applied for diagnosing
and treating electrical disorders of the heart. Catheters are passed via the transseptal route into the left atrium and the left ventricle in order to map the location of abnormal electrical pathway or the sites of origin of rhythm disorders.

In 1962, Dr. Eugene Braunwald was appointed Head of the new cardiology branch at NHI/NIH and he appointed Dr. Ross as Section Head of the cardiac catheterization laboratory. As fate would have it, Dr. Edmond Sonnenblick was also a member of the group at the NHI, at that time studying the mechanics of isolated cardiac muscle. Dr. Ross started applying some of Dr. Sonnenblick’s concepts of preload, afterload and inotropic state to isolated muscle in the context of human disease.

In 1968, Dr. Ross was invited by Dr. Braunwald, who had become the Founding Chair of the Department of Medicine at the newly established University of California San Diego (UCSD), and he remained until his retirement. There, Dr. Ross started a new line of investigation on the pathophysiology of myocardial ischemia and mechanical overload. The NIH launched a new initiative on acute myocardial infarction, and Dr. Ross was awarded a large grant on the topic, which he pursued for decades. The Seaweed Canyon Laboratory, his experimental cardiology facility near the cliffs facing the Pacific Ocean, was established. I joined this laboratory immediately after Dr. Dean Franklin developed a miniature implantable ultrasonic dimension gauge and I took part in Dr. Pierre Teroux’s initial experiments to analyze serial changes in regional myocardial function following occlusion of the coronary artery in unanesthetized dogs. The results of this study differed in several respects from those previously reported in open-chest animals. One of the most striking differences was the effect on normal physiological responses such as agitation because of pain. This model for conscious animals later offered important implications for the influence of therapy on the extent of myocardial damage after myocardial ischemia. In fact, Dr. Ross first demonstrated that coronary reperfusion after prolonged occlusion of a coronary artery was beneficial because it could decrease infarct size. Those experiments laid the basis for subsequent studies in humans.

Then I started my experiments to assess LV function during adaptation to chronic pressure overload produced by an ascending aortic constriction in conscious dogs, instrumented with an intraventricular micromanometer and pairs of ultrasonic crystals for measurement of LV wall thickness and internal LV chamber diameter. The left ventricle responds to chronically elevated pressure by initial dilation with increased wall stress followed by gradual wall thickening and consequent reduction of wall stress to near normal. After successful adaptation to the pressure overload, hypertrophy per se did not produce intrinsic depression of the myocardial inotropic state, in terms of the appropriateness of the matching between afterload and the level of inotropic state, as moderated by the preload. When I first submitted this article to Circulation Research, the referee’s comment was very strict about the term “mismatch” being presumably borrowed from the engineers, but the concept of mismatch between the degree of afterload and the level of contractility seeming to have very little substance to it other than another way of restating the problem. But this word is now used all worldwide and has made it into the dictionary.

In 1982, Dr. Dirk Brusaert from Antwerp, Belgium, spent several weeks with Dr. Ross in La Jolla and the following year Dr. Ross visited Dr. Brusaert. From there, they planned a series of international scientific conferences. In 1987, Kyoto was added as a host site. Between 1984 and 2010 there were 13 Antwerp/La Jolla/Kyoto conferences. I clearly remember the conference in Kyoto in February 2000. It was snowing when Dr. Ross disappeared in the morning and returned just before his talk, which he started with the phrase “I just came back from the Golden Pavilion where I recognized the full worth of the snow scene of Hiroshige”.

So far, there are more than 60 Fellows who were inspired by Dr. Ross in their youth and have been active in the front line of cardiology ever since. I am indeed so proud to be one of those Fellows.