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OBITUARY

In remembrance of Dr. Yukihiko Nosé

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On 13 October 2011, Dr. Yukihiko Nosé (Fig. 1), who made great contributions to developing the US artificial heart program in 1964 and who played a leading role internationally in artificial organ research and development in the last 50 years, passed away at the age of 79 years old. I would like to express sincere condolences to his wife, Ako, and his family.

Dr. Nosé graduated from Hokkaido University School of Medicine in 1957, started his career in artificial organ research at the first Department of Surgery at Hokkaido University in 1960, and then in the same year spent 6 months at the laboratory of Prof. Shigeki Watanabe at the University of Tokyo School of Engineering, the Department of Mechanical Engineering, where he was exposed to study of the artificial heart that had been started in 1959 by young members of the team including Kazuhiko Atsumi and Motokazu Hori et al. at Prof. Kimoto's laboratory. In 1962, Dr. Nosé then joined Dr. Adrian Kantrowitz's laboratory at New York State University's Downstate Medical Center, Maimonides Hospital, to officially start his career in artificial heart research [1]. Two years later in 1964, Dr. Nosé moved to the laboratory of Dr. Willem Kolff at the Cleveland Clinic Foundation (CCF) Artificial Organs Institute where he engaged in research and development of artificial organs, including the artificial heart, artificial kidney, artificial liver, oxygenator, artificial pancreas, neuro-prosthesis, biomaterials, and biomedical instrumentation [2]. At the CCF, starting as a research assistant and research associate, Dr. Nosé quickly climbed to the position of Director of the Institute of Artificial Organs and Chairman of the Artificial Organs Division of the CCF after Dr. Kolff left for the University of Utah in 1967. Along with his research career at the CCF, Dr. Nosé also taught at Case Western Reserve University, where he was appointed Adjunct Professor of Biomedical Engineering. In 1988, Dr. Nosé resigned from the CCF, assuming the position of Emeritus Director of the Artificial Organs Division of the CCF and simultaneously taking the position of Adjunct Professor of Surgery at Baylor College of Medicine, Houston, Texas, which was followed by an appointment as Tenured Professor of Surgery at BCM in 1990. Until passing away this year, Dr. Nosé remained active as the Tenured Professor of Surgery at BCM, making worldwide contributions to artificial organ research and development. In remembrance of Dr. Nosé, this article pays

Fig. 1 Dr. Yukihiko Nosé

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Fig. 2 Dr. Kolff and Dr. Nosé

tribute to his contributions by reviewing his achievements in the area of artificial heart research.

When Dr. Nosé joined the laboratory of Dr. Kolff at CCF in 1964, in the United States clinicians and researchers, including Dr. Michael DeBakey of Baylor College of Medicine and Dr. Willem Kolff of CCF, had been discussing initiating a national artificial heart program. Dr. Nosé and Dr. Hall of Baylor College of Medicine, Houston, TX, helped Dr. Kolff and Dr. Hall's supervisor, Dr. DeBakey, to prepare the national artificial heart program with a 300 million dollar budget for the duration of 10 years. Since that time, the US artificial heart program started to progress together with the space program generated by the late President John F. Kennedy. Thus, it is not an exaggeration to say that Dr. Nosé is the founding father of the US artificial heart program.

Dr. Nosé, who moved to the CCF to the laboratory of Dr. Kolff (Fig. 2), put all his efforts into advancing the diaphragm-type pneumatic ventricular assist device (VAD) and total artificial heart (TAH), the latter achieving the world's longest survival of 145 days in 1974 [3]. It was around this time that Dr. Nosé successfully established a biolization concept using calf skin gelatin to obtain a clot-free blood-contacting surface in artificial hearts [4].

The heart transplantation performed successfully in a human by Dr. Christian Barnard of South Africa in 1965 and the artificial heart program started in 1964 in the United States had advanced hand-in-hand, and the world's first historical bridge to transplantation in humans using the TAH performed by Dr. Denton Cooley of Baylor College of Medicine in 1968 paved the way for artificial hearts as a bridge to heart transplantation. Following this historical event, the National Institutes of Health (NIH) of the United States launched a national program for totally implantable VADs in the late 1970s. In responding to the request for the proposal, Dr. Nosé and the California-based liquid rocket company called Aerojet Co. proposed a high-pressure

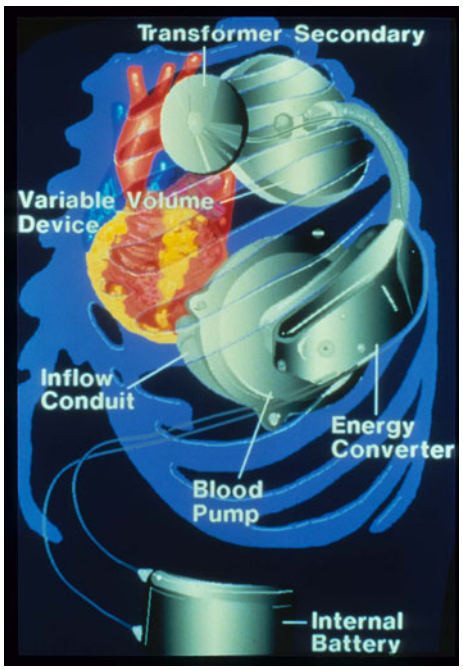

Fig. 3 Design of the completely implantable VAD system

electrohydraulic system that comprised a miniature electrical motor and a gear pump to activate a pusher-plate type blood pump. Dr. Nosé's proposal was accepted by the NIH as one of the four contractors with contract money of over 1.0 million dollars per year [5]. This system included a transcutaneous energy transmission system to allow tether-free operation of the system and an intra-thoracic compliance chamber to compensate for volume changes occurring in the blood side of the implanted pump, offering a completely implantable VAD system (Fig. 3). Utilizing this system, the local infection problem at the site where the power line penetrated the skin in the semi-completely implantable system could be circumvented, and the patients could be tether-free to attain a better quality of life, consequently more efficiently bridging the time to heart transplantation as well as allowing destination therapy in those who are not eligible for heart transplantation. Although the pneumatic version was implanted in patients as a bridge to heart transplantation for a maximum duration of 150 days at the CCF, the completely implantable version had not reached clinical trials in the US, for Dr. Nosé left the CCF in 1989.

In the late 1970s, the TAH design in Dr. Nosé's laboratory was changed from the diaphragm-type pneumatic TAH that Dr. Kolff left behind when he moved to Utah to the pusher-plate type, which could be controlled better, with the aim of developing a completely implantable system. To test the best left–right control mode for a completely implantable TAH system, a versatile control system was designed to run the left and right pusher-plate type

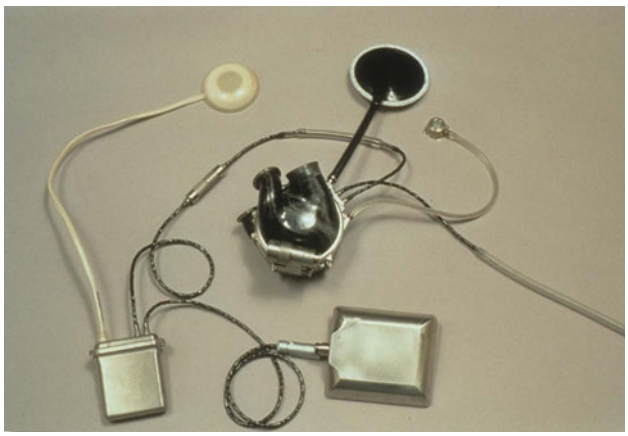

Fig. 4 The CCF's completely implantable electrohydraluic TAH system

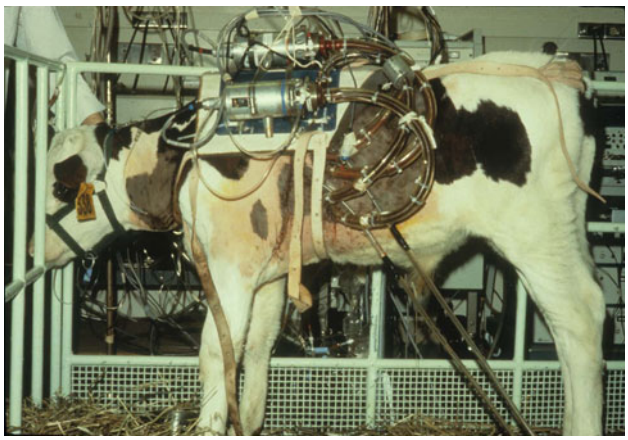

Fig. 5 Nonpulsatile biventricular bypass animal model

blood pumps implanted in calves in various modes. The author of this article had the honor of designing a control system to carry out the study in vivo [6]. The outcome of this physiological study led to designing a completely implantable, left and right alternately ejecting TAH system utilizing an energy converter developed earlier for a completely implantable VAD system, and proposed to the NIH in 1988, resulting in a government contract. Other competitors included the University of Utah, Pennsylvania State University, and Texas Heart Institute, the later achieving a commercially available TAH called AbioCor in 2008. Again, because Dr. Nosé left the CCF in 1989, the CCF TAH (Fig. 4) did not reach clinical trials. Besides utilizing electrical energy, Dr. Nosé worked on a nuclear power-driven implantable VAD system in collaboration with the University of Washington from the 1970s to early 1980s. However, due to fear of contamination by nuclear radiation, the project was stopped in the mid 1980s [7].

As the development of artificial hearts progressed in the mid-1970s, interest in non-pulsatile systems increased because the continuous flow pumps offered a simpler design and longer durability without requiring inflow and outflow valves as required for pulsatile systems. Dr. Nosé's group launched a bi-ventricular bypass study using two continuous flow pumps designed by a company called Hemadyne Co. located in Minneapolis, MN, USA, under ventricular fibrillation to study the effects of pulseless flow on biological systems in the chronic stage (Fig. 5). The author of this article had the privilege of participating in this study starting in 1978. The study attained the longest survivor with 99 days in 1984 [8]. Since the causes of termination were not due to pulseless flow, the continuous flow devices began to receive increased interest as the next generation of mechanical circulatory support devices. This historical event had a great impact on the international community, triggering the development of continuous flow devices and leading to the innovative (1) VAD program started in 1995 by the USA's NIH; in this program, among five projects accepted, three proposed the continuous flow devices, including the HeartMate II, Jarvik 2000, and CorAide; (2) the biventricular or replacement type mechanical circulatory support devices supported by the New Energy Development Agency (NEDO) of Japan, which started in the same year, including the Gyro pump of Baylor College of Medicine (BCM) and DuraHeart of Terumo Co.; (3) the Japan Science and Technology Agency (JST) artificial heart program, which funded the development of a continuous flow pump called EVA-HEART proposed by the SunMedical Co. All these government-supported efforts led to clinical trials in the 2000s.

Dr. Nosé, after retiring from the CCF in 1989, moved to Texas Medical Center to continue the artificial heart research under Dr. DeBakey. In the early 1990s at the Texas Medical Center, the implantation of the pulsatile VAD and heart transplantation was being carried out frequently. The contrast between the American and Japanese technologies was shown by the different circumstances of patients implanted with an electrical VAD HeartMate XVE moving freely inside the hospital and discharged home over the weekends, while the patient wearing Toyobo's pneumatic extracorporeal VAD were confined to the hospital room. The artificial heart projects at Baylor consisted of (1) development of a centrifugal blood pump in collaboration with Nikkiso Co., (2) the one-piece eletromechanical TAH, and (3) the axial flow pump Dr. DeBakey had been working on in collaboration with NASA; the latter resulted in the MicroMedDeBakey VAD, which is currently being used in the clinical setting. The unique, one-piece electromechanical TAH (Fig. 6) was designed based on the anatomical data obtained from 24 heart transplant patients at Methodist Hospital [9]. Although Dr. Nosé proposed obtaining a NIH contract based on the one-piece eletromechanical TAH, two projects, from

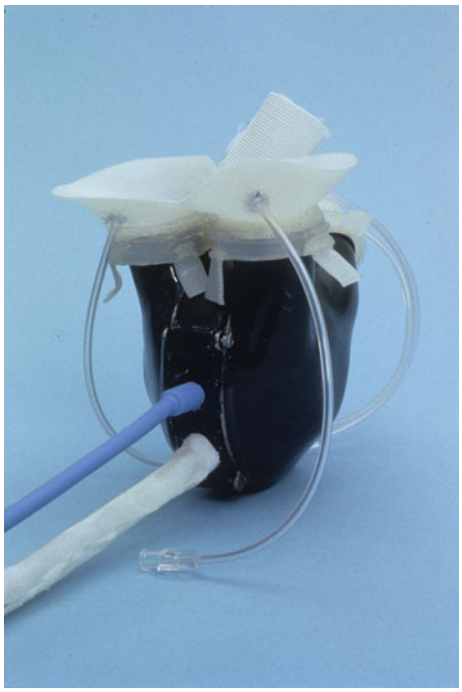

Fig. 6 The unique, one-piece electromechanical TAH designed at Baylor College of Medicine

Pennsylvania State University and Texas Heart Institute, that had been on-going since 1988 seemed to have had priority over the Baylor TAH to continue the second phase animal study from 1992 to 1996; hence, the Baylor TAH did not move forward. Anatomical data were obtained from 24 heart transplant subjects, including the thoracic space after resection of the heart and the excised heart; however, this became the base for designing the clinical TAH AbioCor I that was used in patients in 2001.

As part of pushing the development of continuous flow devices forward, Dr. Nosé organized the 3rd International Symposium for Nonpulsatile Flow Pumps in 1992 by honoring Dr. DeBakey, who had invented a roller pump in 1932, which was followed by the initiation of the International Society for Rotary Blood Pumps (ISRBP) in 1993. The first ISRBP Conference was held in Suzuka, Mie Prefecture, Japan, in 1993. The ISRBP planned to hold annual meetings, rotating among Japan, Europe, and the American continent, to support the fast development, commercialization, and clinical trials of continuous flow devices around the world. This year, the 19th ISRBP meeting was held in Louisville, KY, USA, and made substantial contributions toward the progress of continuous flow technologies and their clinical applications. During the last decade, continuous flow devices have made great progress and have almost replaced pulsatile devices in applications as a bridge to heart transplantation as well as for permanent support of circulation. These advances are

Fig. 7 Nikkiso HPM-15 centrifugal blood pump

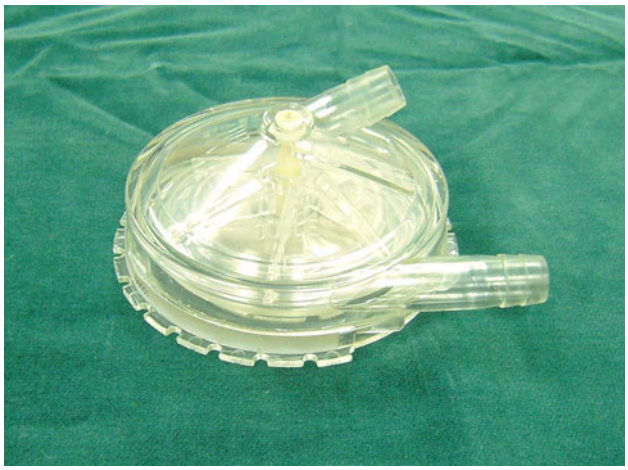

Fig. 8 Kyocera Gyro pump

the result of Dr. Nosé's vision, curiosity, enthusiasm, and continued friendly support.

The research and development programs at BCM after 1993 evolved around the continuous flow pump projects. Particularly, the centrifugal blood pump HPM-15 developed in collaboration with Nikkiso Co. of Japan was approved as a CPB pump (Fig. 7). In the NEDO project that started in 1995, the Gyro pump with Kyocera of Japan (Fig. 8) evolved into a titanium pump and moved to the pre-clinical stage as a biventricular bypass system (Fig. 9). Currently the plastic Gyro pump developed at BCM has been approved for clinical use as a CPB pump in Japan [10]. Dr. Nosé helped develop the Baylor/NASA axial flow pump into the MicroMedDeBakey VAD (Fig. 10), which has been implanted in many patients awaiting heart transplantation in Europe and the USA, and is currently being considered for FDA approval.

Besides being active in artificial heart research, Dr. Nosé did pioneering work to advance technologies in the areas of

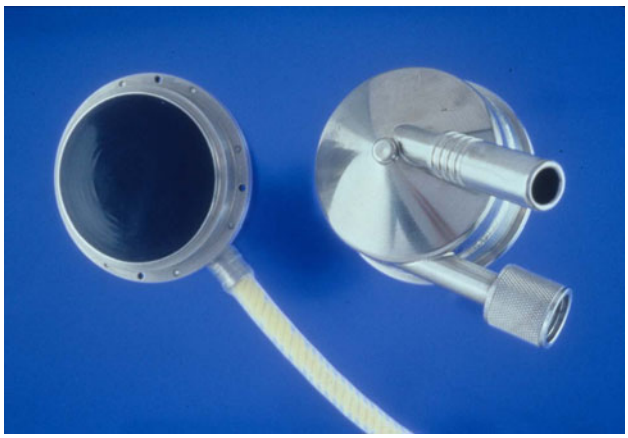

Fig. 9 Baylor NEDO biventricular bypass centrifugal pump

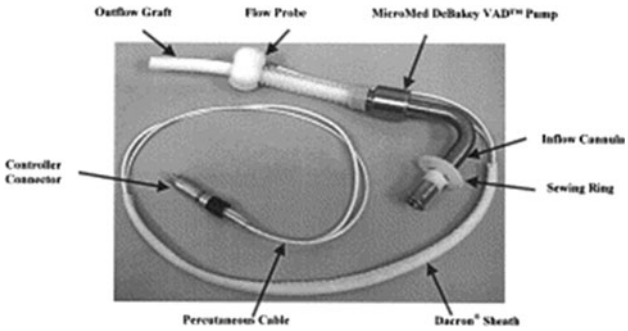

Fig. 10 MicroMed DeBakey VAD

the artificial kidney, liver, pancreas, neuro-prosthesis, and other devices. To promote artificial organ research, clinical applications and education, Dr. Nosé was instrumental in starting international academic societies, centers, journals, and projects, including the International Society for Artificial Organs (ISAO) in 1977; the International Center for Artificial Organs and Transplantation (ICAOT) in 1977; the International Faculty for Artificial Organs (INFA) in 1987; the official journal of the ISAO, Artificial Organs, in 1977, for which he acted as an Editor-in-Chief from 1977 to 1999; the US-USSR Artificial Heart Program; the Hokkaido International Medical and Industrial Complex Project (HIMEX); the International Society for Rotary Blood Pumps (ISRBP) in 1993; the World Apheresis Association (WAA) in 1986; the International Center for Medical Technologies (ICMT) in 2002 in Houston; and many others. Dr. Nosé delivered the 13th Hasting Lecture in 1989 during the NIH Artificial Heart Program Contractors Conference. Dr. Nosé was the Congress President of the American Society for Artificial Internal Organs (ASAIO) in 1993 and was the ASAIO President in 1993. In the long history of ASAIO, Dr. Nosé was the only Japanese scientist to become the ASAIO Congress President. Dr. Nosé published over 1,000 papers related to artificial organs. He educated and influenced over 500 fellows and students around the world during his stay at the CCF and Baylor College of Medicine. Dr. Nosé always challenged new and unknown things, supported by his philosophy of "unlimited curiosity, unlimited enthusiasm, unlimited optimism, and unlimited friendship." It is difficult to accept that we will not see him any more, but his teaching and philosophy live among us eternally. In closing this tribute, I would like to express heartfelt, sincere appreciation to Dr. Nosé, who guided us for a long time. Appreciation is also extended to his wife, Ako, who supported Dr. Nosé in every respect. Dr. Nosé, thank you, and please rest in peace.

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