

A surgeon's quest

M S VALIATHAN

Manipal University, Manipal 576 104, India

(Email, mvaliathan@gmail.com)

This last part of surgery, namely, operations, is a reflection on the healing art; it is a tacit acknowledgement of the insufficiency of surgery. It is like an armed savage who attempts to get that by force which a civilised man would get by stratagem.

John Hunter

[Palmer John (ed.) 1835 *The works of John Hunter*, Vol. 1 (London: Longman)]

[Valiathan M S 2008 A surgeon's quest; *J. Biosci.* 33 313–326]

1. Introduction

The surgeon is generally regarded by the intelligentsia of science and medicine as a mechanical craftsman if not “hewer of wood and drawer of water”. Surgery has always been a practical art, the treatment of disease by manual processes, and the education of a surgeon, as that of any craftsman, has been by apprenticeship through the ages. But as noted by Hunter – the founder of the scientific basis of surgery – a surgeon is more than an operator, does more than repetitive work and adds something of his own to the store of knowledge he received. And adding something to knowledge can scarcely happen except through enquiry into problems he may have encountered at the bed-side.

I should dearly love to say that I wished to become a surgeon when I was a school boy and that I had enjoyed dissecting dead frogs and looking after sick animals. But I grew up with no such ambition and no clear goal. My family tradition in medicine had been strong for over two generations and a grand uncle who studied medicine in Edinburgh in 1902 had long been our hero. It was therefore natural that I grew up on an unstated assumption that I would follow the family tradition. The die was cast in 1951 when I joined the first batch for MBBS in the Trivandrum Medical College. Medical education is so overregulated and overburdened with examinations that medical colleges in India lack the intellectual climate for research except

when a great teacher kindles the spirit of enquiry. I was fortunate to have one in Professor Thangavelu who taught us pathology. While taking a class on inflammation, he once questioned us on the reaction of pus. Some of us voted for acidic, others for alkaline, and the non-aligned preferred neutral. He listened patiently and said “I know you will go to the library this evening and look up text books to find the answer to my question. Let me tell you there is a better way to find the answer. You take litmus paper with you when you go to the wards tomorrow and check the reaction of pus in several patients; also look at the diagnosis and reports of bacterial culture. You would then know that the reaction can vary and the cause too can vary”. Listening to him, the scales fell from my eyes, and I saw at once that the pursuit of knowledge would not be possible without the use of one's mind and experiment; what was gained in the absence of one or both was an illusion of knowledge. I never forgot that lesson.

2. Liver function studies

My introduction to scientific enquiry was incidental to my surgical training. As a medical student in Trivandrum and surgical trainee in Liverpool, UK, I had observed the devastating consequences of cirrhosis of the liver which is a common malady. The patients in Trivandrum approached the hospital when their scarred liver had blocked the entry of

Keywords. *Ayurveda*; endomyocardial fibrosis; prosthetic heart valve; thrombo-resistance

Abbreviation used: BARC, Bhabha Atomic Research Centre; EMF, endomyocardial fibrosis; GBH, graphite-benzalkonium-heparin; IEC, Institutional Ethics Committee; IIT, Indian Institute of Technology; NAL, National Aerospace Laboratory; PVC, polyvinyl chloride; ULMW-PE, ultra high molecular weight polyethylene

venous blood and raised the portal venous pressure so high that they bled profusely from venous “varices” in the esophagus; alternately, they would come when the scarring had blocked the exit of blood from the liver, with massive exudation of fluid in the abdomen called ascites. While bleeding ended life quickly, ascites drained it away by degrees. Both assured certain destruction. When I had to choose a topic for fulfilling the research component of the Ch.M degree of the Liverpool University in 1960, I sought the advice of Professor A K Basu of Kolkata who was a reputed authority in the newly emerging field of portal hypertension. He promptly suggested the role of secondary hyperaldosteronism in the perpetuation of cirrhotic ascites for my study. On the recommendation of Professor Wells, my teacher in the University, I was awarded a Fellowship in the Department of Dr John Gibbon of the Jefferson Medical College, Philadelphia to carry out my research and my immediate supervisor was Dr Walter Ballinger who was a strong proponent of surgical research. In reviewing the literature, I soon found that the removal of the adrenal glands had been done in intractable ascites in some two dozen patients on the expectation that adrenalectomy would rid the patient of hyper aldosteronism and relieve him of ascites. However the patients continued to have ascites after the operation even though the accumulation of fluid in the abdomen had decreased. In other words, the tendency to retain sodium and water in the abdomen had been curtailed, but not eliminated, by the removal of the adrenal glands. What else could be responsible for the perpetuation of ascites? Arguably, the liver itself could have a role because it was known that obstruction to the exit of portal venous blood from the liver was immediately followed by ascites in certain clinical syndromes and in the experimental model. It was therefore logical that liver would be part of an array of body mechanisms to retain salt, an array which evolved as life moved from the sea to land and the conservation of salt in the body became essential for survival. The role of the liver could have become dormant as more potent mechanisms such as the one involving aldosterone emerged but its atavistic role could reassert itself if and when the newer mechanisms disappeared. I tested this hypothesis in a canine model of experimental ascites and wrote my thesis for Ch.M on the basis of the study, which was also published (Lalonde *et al* 1964). My hepatic obsession continued when I returned to India and joined the faculty of the Postgraduate Institute of Medical Education and Research, Chandigarh which was in its infancy in those far off days. Professor Aikat who headed the Department of Pathology had observed with Iber and others earlier in Kolkata that portal hypertension could develop in the absence of cirrhosis and with apparently normal liver-function tests in a condition called “non-cirrhotic portal fibrosis”. It did not take long for us to spot this syndrome in Chandigarh and hold discussions on its causation, pathogenesis and management. When I

raised the possibility that the normal values in biochemical tests could have more to do with the large reserve capacity of the liver than with the status of liver function, and that an electrophysiologic test of the liver might give more accurate information on liver dysfunction, Professor Aikat was amused. Given my limited knowledge of electrophysiology, I imagined that the electrical activity of hepatic cells in the fantastically active organ would summate and produce a measurable electro-hepatogram. I found no support for this idea among my colleagues including a biophysicist who did not welcome a surgeon’s intrusion on his turf. As I was an admirer of J B S Haldane, who respected no intellectual boundaries and was a physiologist at one stage, I sought his response on the possible existence of an electro-hepatogram. Haldane who was seriously ill replied a few months later (figure 1).

However by mid 1964 my interest in liver disease and general surgery as a whole was yielding place to the pull of cardiac surgery which was making dramatic progress and giving new life to children and those with valvular heart disease. The seed had been sewn during my tenure at the Jefferson Medical College where Gibbon had made history by developing a heart-lung machine during two decades of innovative experimental work. He had demonstrated for the first time in 1953 that the machine could be used successfully in a clinical open heart operation to close an atrial septal defect. The saga of Gibbon’s endeavour had made as profound an impression on me as had his unfailing consideration and encouragement to surgical residents and Fellows like myself. It was therefore with much excitement that I welcomed the opportunity to join the Department of Cardiac Surgery at the Johns Hopkins Hospital as a Fellow of Dr Vincent Gott prior to my move to the George Washington University for clinical training in cardiothoracic surgery. Though my laboratory schedule was heavy, Dr Gott gave me time and facilities to pursue my old interest in the electro-hepatogram as a collateral activity at the Hopkins. The study showed that the canine biliary tract was electrically positive with reference to the liver capsule, and potentials ranged between 3 to 15 mv. Intraportal infusion of dextrose and insulin caused a brief fall in potential followed by a sharp increase (Valiathan *et al* 1967). These results vindicated Haldane’s belief that measurable electrical activity in the liver “would be associated with biliary secretion rather than more important metabolic activities”. That paper marked my farewell to studies on the liver.

3. At Johns Hopkins

3.1 *Blood compatible materials*

The next chapter as a Fellow at the Johns Hopkins University with Dr Gott as my mentor was a turning point

GENETICS AND BIOMETRY LABORATORY
GOVERNMENT OF ORISSA
BHUBANESWAR 3
ORISSA, INDIA

No.64/0063.

April 27, 1964

Dear Dr. Valiathan,

I have just got your letter of October 14, 1963, as I have only recently returned here after a series of operations for cancer in England. I have no doubt that there is electrical activity in each hepatic cell. However there is no reason to think that such activity is synchronized in different cells; nor is their arrangement such that one would expect the activities of different cells to summate. They might largely cancel out. If anything definite were found, I should expect it to be a fairly steady potential difference associated with biliary secretion rather than more important metabolic activities. On the other hand the gall bladder is contractile. I should guess that you were more likely to get an interpretable electrocholecystogram than an electrohepatogram. But my guess is worth little. If you do find an electrohepatogram you will, I think, have revealed a coordination of the liver cells which I should not have expected. As the liver perhaps regenerates faster than any other tissue, it could be a very favourable site for investigating electrical phenomena connected with regeneration.

I am the last person to give you advice. I have not kept up with that kind of physiology seriously since 1922, or at all since 1932. I hope that by now you have had some success in your work.

Yours sincerely,
J.B.S. Haldane
(J.B.S. Haldane)

Dr. M.S. Valiathan,
Department of Surgery,
Institute of Postgraduate Medical Education & Research,
Chandigarh,
Punjab.

Figure 1. Haldane's letter.

in so far as it influenced my approach to cardiac surgery and the course of my life itself. Warm hearted and gentle, Gott was generous to a fault and too self-effacing to mention his brilliant background in the University of Minnesota as a trainee under Dr Lillehei. He was a key player in the path-breaking advances – there were many – which took place in Dr Lillehei's outstanding programme which nurtured a generation of world leaders in cardiac surgery. He came to Hopkins with a formidable reputation from the University of Wisconsin where he had made the serendipitous observation that heparin would bind to rigid materials and make their surface blood compatible provided they had been treated earlier with colloidal graphite and benzalkonium chloride sequentially (Gott *et al* 1963). His observation became a trail blazer because no fewer than 20–25 surfaces with the wall-bonding of heparin and other molecules emerged in the following two decades. It seemed to offer new hopes

for replacing damaged heart valves and diseased arteries, the demand for which had become insistent following the advent of open heart surgery. However the new materials sought had to possess far greater and more durable blood compatibility than what siliconised materials had provided till then. In an attempt to reduce clot formation on artificial heart valves, Gott had evaluated a number of materials in the highly thrombogenic environment of the canine vena cava. Not surprisingly the rings made of different materials were partly or fully filled with clots in a few hours: the surprise was the fact that rings of methyl methacrylate coated with graphite stayed open for as long as 14 days. This was initially attributed to the physical properties of colloidal graphite such as smoothness and negative zeta potential but subsequent studies revealed that the graphite-benzalkonium-heparin (GBH) surface owed its thrombo resistance to the ability to bind heparin following exposure to a cationic

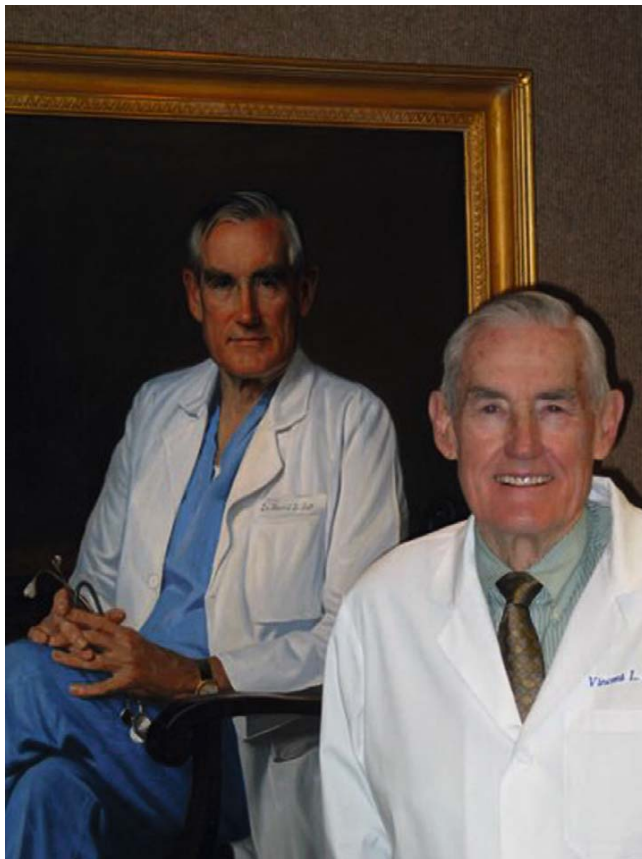


Figure 2. Dr Vincent Gott at Johns Hopkins, 2008.

surface active agent, benzalkonium chloride. Thanks to the adsorptive property, graphite bound the cationic detergent which has surface active properties, and the positively charged ammonium radical on the cationic detergent in turn, bound heparin which is a polysaccharide containing three negatively charged sulphate groups per unit. In spite of the bond being ionic, heparin was sufficiently stable to withstand the systemic challenge of protamine which is routinely used for neutralizing heparin in open heart surgery (Whiffen *et al* 1964). I was deeply involved in the experimental evaluation of the GBH surface by the implantation of leaflets and rings, which confirmed its thrombo-resistance. In an expanded study where specially fabricated rings of polymeric materials, stainless steel, silicone and GBH coated polycarbonate were implanted in the inferior vena cava, the uncoated rings clotted in two hours whereas the coated rings stayed open for two weeks (Gott *et al* 1968). The junction between a prosthetic valve and the inner layer of the heart was a special focus of our investigations as thrombosis seemed to begin at that interface (Valiathan *et al* 1966). The junction between the endocardium and a prosthetic material or between bone and a ceramic – between, in fact, the living and non-living, continues to remain vulnerable in all implants. A molecular union between the living tissue and a prosthetic material would revolutionise the history of bio-implants. It remains the Grail of tissue engineers.

While the thrombo-resistant property of GBH was no longer in doubt, we were aware of its drawbacks such as the durability of the heparin-bonding being limited to hours

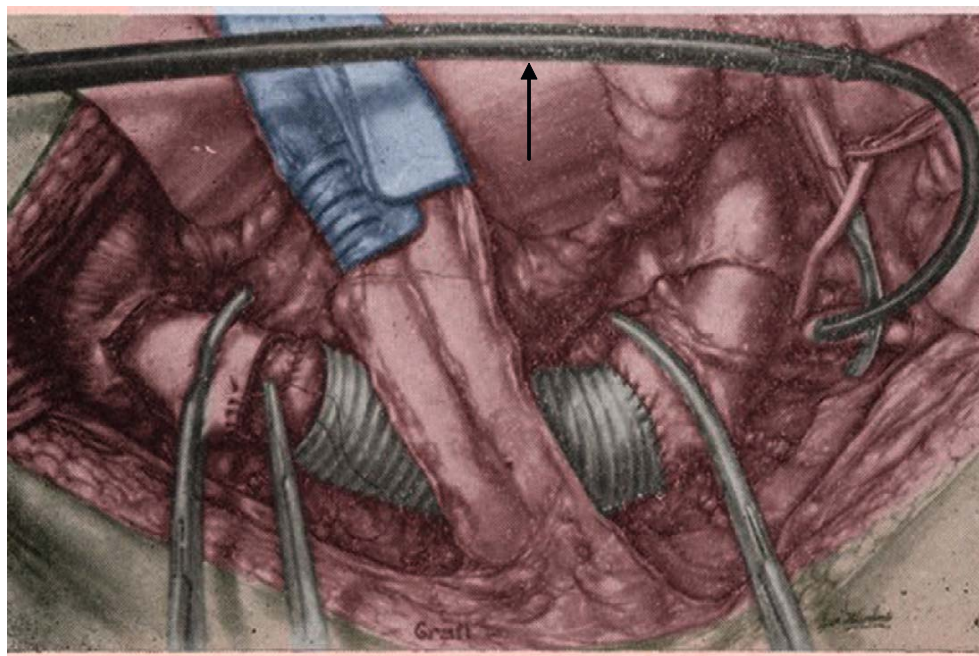


Figure 3. Aneurysm of the thoracic aorta, view from the left chest after resection; the black, GBH coated shunt (arrow) can be seen.

rather than days; poor tolerance of the semi-rigid GBH-coated surface to repeated bending or the application of surgical clamps. These drawbacks did not stop its application in an experimental double-chambered artificial heart designed by our group (Topaz *et al* 1967) and a simplified technique for resecting thoracic aortic aneurysms. These aneurysms grow progressively and result in fatal rupture unless they are resected early and reconstructed with a vascular graft. But resection posed serious dangers due to the temporary interruption of blood flow through the aorta, which was required to carry out the surgical procedure. The dangers included the sharp elevation of blood pressure above the level of interruption and deprivation of blood supply to the spinal cord and kidney below the interruption. To prevent these complications, the technique in the early sixties employed a temporary left heart bypass, complete with the suspension of coagulation in the patient by heparin injection, insertion of a temporary shunt between the left atrium and femoral artery, and the use of an external pump. This was a cumbersome and difficult procedure as the deliberate suspension of coagulation caused troublesome bleeding. We recognised that a temporary shunt from the aorta above the level of the aneurysm to a downstream location would do the job just as well provided the shunt would remain thrombo-resistant during the two or three hours of the procedure for resection and grafting. GBH met the requirements admirably and, after much experimental work, a GBH-coated shunt was used successfully for resecting aneurysms of the thoracic aorta at the Hopkins (Valiathan *et al* 1968, figure 3).

A non-graphitised, heparinised version of the bypass system known as "Gott shunt" was commercialised in later years. My Fellowship under Gott at the Hopkins was one of the happiest and most productive periods in my life as a surgeon and investigator (Valiathan 1969). There is something in the air at Hopkins, which never fails to recharge one's mind.

4. At the Georgetown University Hospital: from materials to devices

My Fellowship in thoracic surgery at the George Washington University Hospital, Washington DC under Dr Brian Blades who had done the first dissection lobectomy of the lung in the nineteen thirties was followed by training in cardiac surgery under Dr Charles Hufnagel at the Georgetown University Hospital in the same city (*see figure 4*).

Hufnagel was a legendary figure. In 1947 he had used highly polished methyl methacrylate tubes for the permanent intubation of the thoracic aorta in dogs and developed an ingenious "multiple point fixation" to fix the tube to the aorta in 2–3 min without stitches or continuous circumferential pressure on the aortic wall. By 1950, he had developed a workable ball valve prosthesis. The cage of the valve in which the ball moved up and down was constructed



Figure 4. Dr Charles Hufnagel with the author during a visit to the Chitra Institute, 1985.

of highly polished methyl methacrylate and the ball was hollow and made of plexiglass. After 100 experiments in dogs, he was sufficiently confident and encouraged to place the valve in a patient ill with aortic regurgitation in September 1952 before the advent of heart-lung bypass. It was a landmark event and by 1954 twenty three patients in advanced condition had been treated with results far superior to those of medical treatment. Apart from his surgical skill and innovative mind, Hufnagel was a supreme individualist who insisted on using a ventricular pump, micro-crimped vascular graft, disc oxygenator and so on which were designed by him and made according to his specifications! He was a hard task master who never suffered fools gladly. When I joined his service in 1967, he was still at the peak of his powers and had developed a new "unitized, trileaflet valve" for replacing the diseased aortic valve. My years with Hufnagel as a Fellow and later, as an Instructor initiated me into cardiac surgery and gave me an inside view of the engineering of cardiovascular devices. The background at Hopkins with blood compatible materials was an invaluable asset which enabled me to take to the development of a prosthetic heart valve and other complex devices at the Georgetown University as a duck takes to water. I resembled an actor rehearsing a role in full vigour without the faintest idea where my play would be staged.

5. A stop at Indian Institute of Technology, Chennai

On returning to India against Hufnagel's warning – "The Indian virus will destroy you" -, I had an uncertain start. I began my migrant career at the Safdarjung Hospital, Delhi which taught me the ground realities of thoracic surgery in India and how to deal with tough problems such as children in severe distress from acute staphylococcal empyema and

a Hb level of 7 g/100 ml, which had never confronted me abroad. There was no possibility of doing cardiac surgery or doing research at Safdarjung, which would have been inappropriate in any case when emergency services in thoracic surgery were inadequate. My next stop was Indian Institute of Technology (IIT), Chennai where Dr Arcot Ramachandran offered me a Visiting Professorship with permission to operate in the Railway Hospital, Perambur thrice a week. My assignments in IIT included teaching a course in physiology, contributing to seminars and interacting with MS students whose projects covered nearly everything in medical sciences. I was however disappointed that R&D received low priority in the IIT scheme of technical education; a student could spend three years on modelling the aortic valve without getting any closer to making a prototype. As the students were bright and keen, there was no reason why each well conceived project could not have led to a product. Needless to say, my heart valve concept made no progress during my IIT interlude.

6. Chitra Institute, Thiruvananthapuram: TTK Chitra valve

As in the affairs of men, there is a tide in the life of ideas, and the upswing of the valve project coincided with my move to the Sree Chitra Institute, Thiruvananthapuram in 1974. "Institute" was a misnomer because it had a building with incomplete facilities, no furniture or equipment, and a staff of exactly five consisting of security and secretarial personnel! However, I knew instinctively that the stage was set and I had to perform a role for which I had rehearsed in faraway US. Side by side with the commissioning of a speciality hospital, I submitted a project for the development of titanium and polyvinyl chloride (PVC) for medical applications with Ramaseshan of the National Aerospace Laboratory (NAL), Bangalore and Gowarikar of Vikram Sarabhai Space Centre (VSSC), Thiruvananthapuram as collaborators. The project was aimed at developing titanium for implants including a heart valve and PVC for a variety of disposables such as blood bag and oxygenator. Following the approval of the project by the Science and Engineering Council (SERC), I brought two biomedical engineers as Research Fellows to the Chitra Institute, including Bhuvaneshwar who was a bright student of mine at the IIT and is currently the Head of the Biomedical Technology Wing of the Chitra Institute.

The development of a valvular prosthesis which had been a technological challenge acquired moral overtones when the Chitra hospital opened its doors to patients. The Indian Council of Medical Research (ICMR), New Delhi had reported in a working paper that 6 out of 1000 children between 5 – 15 years in India were susceptible to rheumatic fever, which put the young population at risk to valvular heart disease at over a million. While prophylaxis at the

level of the community was the ultimate answer to this huge problem, we were flooded with patients who urgently needed valve replacement, but were too poor to pay for the valve. Nothing was more painful or more cruel than the denial of a surgical procedure to a patient on the ground that a life saving device was beyond his or her means. The failure to reach out to the suffering on the ground of economics was a violation of the basic goal of medicine "for the good of many, for the wellbeing of many". Soon we put together a small group with Bhuvaneshwar as the principal investigator to develop a prosthetic valve of tilting disc design which would fully conform to the ISO 5840 standards. The team included Neelakantan Nair who organized a Tool Room which could fabricate the metallic components of the valve; and Arthur Vjayan Lal, a veterinary surgeon, who put together the animal care facility and operating room where heart valve replacement could be done in sheep with predictable survival. Ramani who joined later as the Head of the Biomedical Technology Wing was an excellent engineer who provided constant support through creative monitoring and trouble shooting. Ramaseshan kept a benign watch over the R&D efforts and came to our rescue in times of crisis with innovative suggestions.

The TTK-Chitra valve which is currently marketed, has been implanted in over 26,000 patients and is said to claim over a third of the Indian valve market (figure 5a). It costs a third of the price of imported valves of similar design and has penetrated markets in developing countries such as South Africa and Bangladesh. The company has recently built an expanded manufacturing facility which should comply with European norms leading to "CE" certification and produce up to 10,000 units a year. This successful valve (model 4) stands on the foundations of three earlier models which failed and caused our group no little disappointment. Therein lies a tale of setbacks, struggle and the resolve not to quit.

A prosthetic valve has three parts, a metallic housing; a disc or ball which functions as an occluder; and a sewing ring of plastic fabric (table 1).

In model 1, the major and minor struts were electron-beam welded and the valve was expected to withstand 360 million cycles of disc movement in the accelerated wear tester, which would correspond to what a natural valve does in the heart during a 10 year period. To our dismay, the major strut fractured at the weld after a mere 100,000 cycles (figure 5b). Thanks to Dr Valluri, the fracture was studied in the NAL; it turned out that weld embrittlement was the cause of fracture. It was clear that titanium welded components were inherently unsafe in the high-fatigue, high-stress location of a heart valve, and the housing had to be integrally machined to eliminate this structural weakness. Additionally the polyacetal disc in the model absorbed 0.5% moisture with a small dimensional change, which was reversible but disturbing. In model 2, the disc was made of single

Table 1. Evolution of valve models

Valve model	Housing	Disc	Sewing ring	Cause of failures
1.	Titanium (welded housing)	Delrin	Polyester	Weld failure. Water absorption by delrin
2.	Titanium (integral housing)	Sapphire	Polyester	Wear of struts. Disc escape
3.	#Haynes alloy + Titanium nitride coating	Sapphire	Polyester	Fracture of disc.
4.	Haynes alloy	*UHMW-PE	Polyester	Successful.

#Haynes, cobalt based superalloy.

*Ultra high molecular weight-polyethylene.

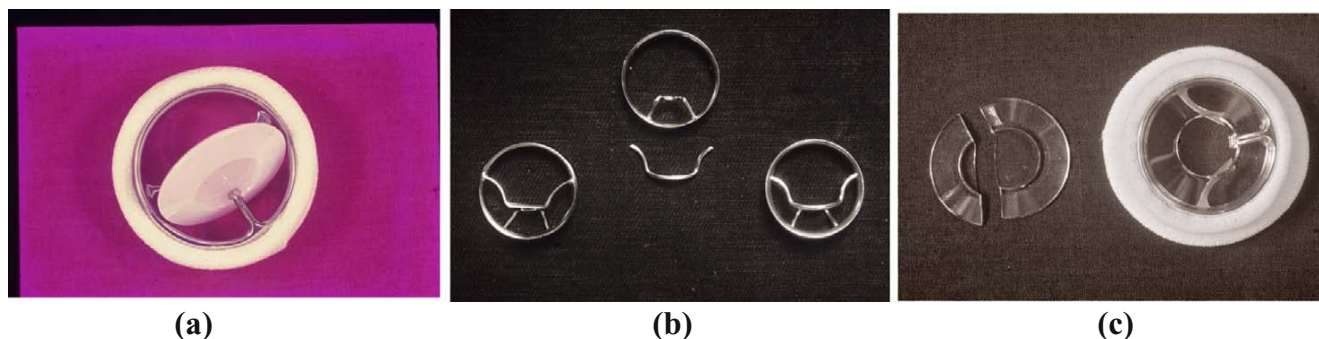


Figure 5. (a) TTK - Chitra valve in current use (model 4). (b) Fractured stent (model 1). (c) Fractured disc (model 3).

crystal sapphire which was inert and blood compatible. The new all-integral cage required the development of new fabrication process, in which the housing was carved out of a block of titanium. This was achieved by the innovative use of conventional and copy-milling techniques. This model failed because of the extensive wear of titanium struts and the escape of the disc. We were intrigued that the wear did not occur in the accelerated wear tester and came to light only in the animal model. We discovered the hard way that glycerol in the wear test chamber had acted as an excellent lubricant and prevented the wear! Model 3 had a housing made of a high wear-resistance aerospace superalloy, called "Haynes-25" (a cobalt based alloy with chromium, nickel and tungsten) – harder to machine than titanium – which was coated with titanium nitride to match the hardness of the sapphire disc. The integral-cage was machined from rods of this very difficult-to-machine alloy using CNC wire-cut and electric-discharge machining (EDM). This model went through all the tests successfully and several sheep were alive and well for months with the valve in their mitral position. In fact, we decided to seek the approval of the Institutional Ethics Committee (IEC) for its clinical trial in late 1986, when disaster struck and one animal which had valve replacement three months earlier dropped dead suddenly. Necropsy showed that the sapphire disc had fractured (figure 5c). We were faced with a major crisis after a decade of toil, when critics including the media did not spare us or our effort. Our group held urgent discussions in consultation with Ramaseshan and decided to give up

not only sapphire but rigid discs altogether. Mashelkar of National Chemical Laboratory (NCL), Pune suggested five new plastic candidates which we screened through improved techniques for wear resistance before choosing ultra high molecular weight polyethylene (UHMW-PE) for making the occluder of the current model (model 4). Fabrication of the disc from UHMW-PE was no easy task because we were demanding no less than a marriage of the unbreakability of rubber with the polish of a mirror in the new disc! The blanks had to be cut from the plastic rods under cryogenic conditions, disc machined, and thermal polishing done in a stainless steel die with controlled heating and cooling cycles even as a uniform compressive load was applied. The flash generated during this process had to be removed with a polished tool under cryogenic conditions again. It took eighteen months to standardize this process cycle and attain the required quality finish and dimensional control of the disc in model 4, which was largely accomplished by a young engineer Muraleedharan who had joined Bhuvaneshwar. In design features, hydrodynamic tests, accelerated durability tests and trials in sheep, model 4 performed extremely well and compared favourably with the Bjork-Shiley standard disc valve which was used internationally at that time. The choice of a soft disc gave model 4 the additional advantages of low impact forces, less potential for cavitation and low closing sounds. Bhuvaneshwar and team showed remarkable skill in designing and fabricating a pulse duplicator which measured the hydraulic performance of candidate valves, and an accelerated tester which tested the wear and

durability of valves through 400 million cycles. When Laser Doppler Anemometry to measure the velocity flow profile could not be set up due to budgetary constraints, his group developed an effective alternative – Pulsed Ultrasound Doppler Velocimetry. Innovation was not in short supply at any stage of the valve project (Bhuvaneshwar *et al* 1983, 1991a, b, 1996, 1991).

After the clinical trial of the valvular prosthesis was approved by the IEC, the first valve was implanted on 6th December 1990 in a 38 year old teacher with aortic insufficiency who did well and is currently running a cyber cafe in Kerala. After 40 valves were implanted at the Chitra Institute with good results, IEC approved the multicentric trial of the valve in five other major centres in India (Sankar

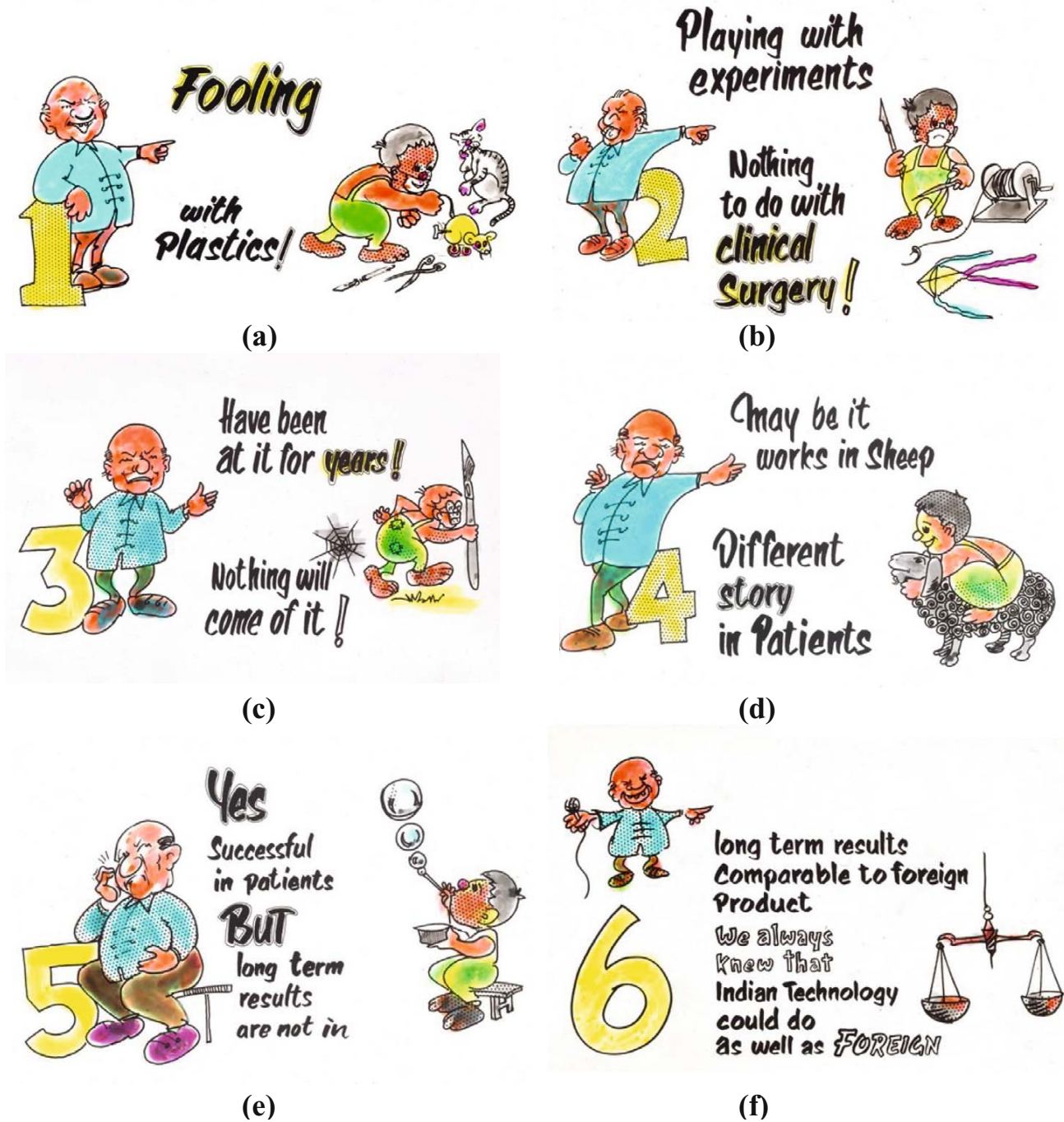


Figure 6. Six cartoons indicating the changing perceptions on the development of Chitra valve.

Kumar *et al* 2001). Ramani played a key role in producing 350 clinical quality valves for the multicentric trials in the Techno-prove facility of the Chitra Institute in association with TTK, when the production process was standardized, QC/QA protocols developed and technology transfer done effectively by giving hands-on training to TTK personnel.

Though Chitra Institute was the lead institution which conceptualized and developed the valvular prosthesis, its development would have been impossible without the support and expert assistance of several institutions including the National Aerospace Laboratory; Hindustan Aeronautics; Government Tool Room and Training Centre, Bangalore; South India Textile Research Association; National Chemical Laboratory; and the major hospitals listed in Bhuvaneshwar *et al* (1996). Far from the Indian stereotype of fatalism and indifference to suffering, the Chitra valve story brought home to us the core of goodness in Indians and their willingness to go the extra mile to help patients with serious illness. As our endeavour unfolded over a decade, it was greeted by a range of changing perceptions by the medical intelligentsia and media. They were captured at that time in a series of cartoons by Joy, who had a ring side view as the Institute's medical artist (figure 6).

The work of the multidisciplinary group at the Chitra Institute was not limited to the TTK-Chitra valve. During the same period, they developed and transferred for successful production a series of devices including a blood bag, disposable oxygenator, cardiotomy reservoir, polyester vascular graft, hydrocephalus shunt and dental composites.

The family of Chitra devices formed the nucleus of a self-regenerating base of medical technology conforming to international standards in India.

7. Soil in the heart

As the Technology Wing of the Chitra Institute quivered with excitement, its hospital counterpart was not far behind. In the nineteen sixties, a former classmate of mine, Professor C K Gopi, had observed in Thiruvananthapuram a heart disease among poor children, which resembled a malady reported from Uganda by Professor Davies a decade earlier. Severely malnourished and short of breath, the children had a puffy face, engorged veins in the neck, protuberant belly and emaciated legs. Treatment was ineffective and no more than 20% survived five years after the onset of symptoms. The careful autopsy studies of Davies had shown the growth of a leathery, fibrous layer inside the pumping chambers of the heart, which progressed relentlessly and reduced the chamber size (figure 7). Furthermore, the fibrous growth stiffened the heart muscle which could no longer relax fully, and ultimately trapped and destroyed the valves between the atrial and ventricular chambers. Other organs were spared except secondarily as a consequence of heart failure. The cause of the disease – endomyocardial fibrosis (EMF) – was a mystery and speculations abounded.

As the outlook for medical treatment was poor and patients desperately ill, we adopted a surgical technique

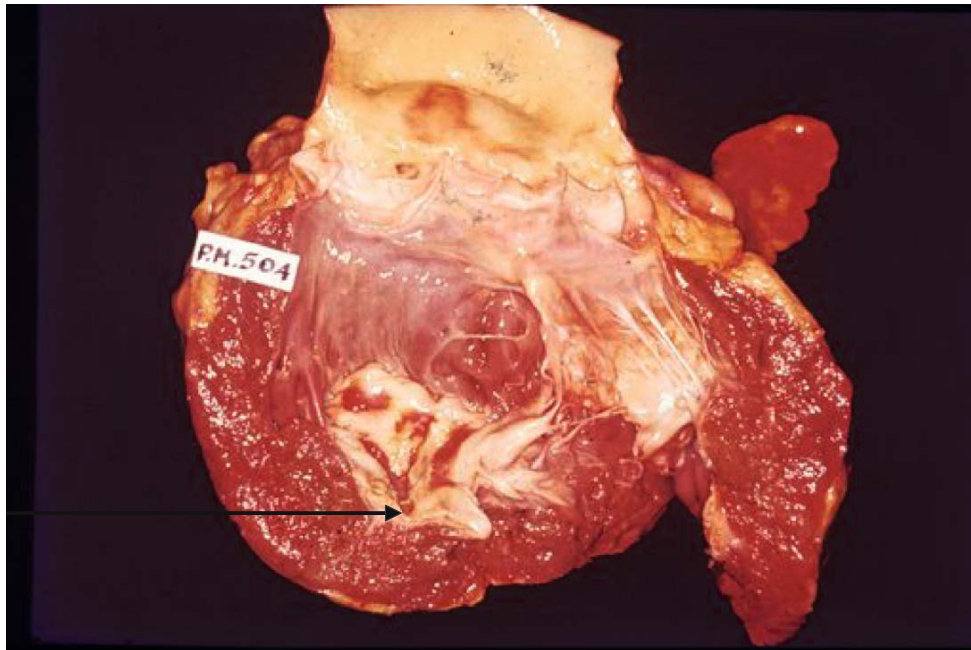


Figure 7. Interior of the left ventricle laid open at necropsy. Note the dense, white scar tissue (arrow) which progressively limits the chamber size of the ventricle and restricts the relaxation of the muscle.

developed by a French surgeon – Dubost – for his patients with EMF from the Ivory Coast. The procedure consisted of cutting out the fibrous layer in the heart and replacing the diseased valves by an open heart operation. Though the operation carried a high mortality of 15%, 60% of the survivors were alive at the end of five years, which was clearly preferable to the doom of medical treatment. In a decade we had the largest surgical series of EMF in the world including those reported from Ivory Coast and Brazil (Valiathan *et al* 1987).

In the nineteen eighties the reigning hypothesis on the causation of EMF was advanced by a British pathologist, Olsen, who claimed that the fibrous overgrowth in the heart in EMF was triggered by the breakdown products of eosinophils. Eosinophil count rises with all kinds of parasitic infections like filariasis in the tropics, and it seemed natural to Olsen that countries like Uganda would face the consequences of eosinophilia – the cardiac damage in EMF being possibly one of them. He was led to this hypothesis by his experience with a special kind of adult eosinophilia in Europe, which was associated with massive elevation of eosinophil count, rapid onset of a systemic illness and, in the terminal stage, morphological changes of the heart similar to those in EMF. This hypothesis of Olsen had been repeated in textbooks and journals so often that it had become a dogma among cardiologists. In a pathetic display of poor self-confidence, pathologists from countries where EMF was prevalent were sending tissue samples to London for histopathologic interpretation! We were, however, in for a series of surprises as our studies got under way. In the first place, patients with EMF had eosinophil counts which were

no different from those of the common people in Kerala. Secondly, eosinophil proteins could not be detected by immunofluorescence in the heart tissues removed during operation. Thirdly, we discovered that the highly endemic areas for filariasis in India such as Tanjore and Orissa where one would have expected a high incidence of EMF, were conspicuous by the absence of the disease. Throughout these exciting studies on EMF, I worked closely with Drs Kartha, Renuka, Shivakumar and Eapen, whose expertise in pathology, cell biology, biological chemistry and analytical chemistry were critical to the investigations.

8. Geochemical basis of EMF

As the fallacy of Olsen's hypothesis became clear, we took a closer look at the global picture of EMF. We found that of nearly nine hundred authentic cases of EMF reported from all over the world, more than eight hundred and fifty belonged to Nigeria, Uganda, Ivory coast, Tanzania, Kerala, Brazil and Venezuela. These far-flung spots on the map had one thing in common - they fell within 15% of the equator (figure 8). The only other common feature among them was poverty of varying degrees. Any hypothesis on the causation of EMF, we reasoned, had to take into account the twin realities of geography and poverty.

What united the countries of the tropical belt were soil and climate: so at any rate we were told by the earth scientists. The well known examples of lung fibrosis caused by silica, asbestos and other substances also prompted us to look to the soil of Kerala for fibrogenic elements as a possible cause



Figure 8. Global map: Pattern of distribution of reported cases of endomyocardial fibrosis (EMF) in 1982-85; the prevalence stood out in Ivory Coast, Nigeria, Uganda, Tanzania, Kerala, Brazil, and Venezuela.

for the fibrosis in the heart. Rich in minerals, tropical soil contains a large variety of elements and their detection in tissue samples called for highly sophisticated methods of analysis. We were fortunate to receive excellent support in elemental estimation from the Centre for Earth Sciences, Thiruvananthapuram, Defence Metallurgical Research Laboratory, Hyderabad, Bhabha Atomic Research Centre (BARC), Mumbai and Indira Gandhi Atomic Research Centre, Kalpakkam.

Over the next few years, we analysed the cardiac tissue samples from patients for a variety of elements in the physiological, trace and toxic categories. Their concentrations were compared with those in cardiac tissues collected from 'controls' who consisted of subjects dying from accidents and undergoing medico-legal autopsy. A trend became visible in three years: the cardiac tissues from patients showed a lower concentration of magnesium and a higher level of thorium than the control samples (Valiathan *et al* 1986). In the initial estimations, BARC reported the concentrations for thorium and indicated the value for all other rare earth elements clubbed together as 'RE'. As soon as we noted the higher concentration of thorium, we looked into the distribution of thorium in Kerala and found that monazite, one of the important minerals of Kerala, contains 8% thorium whereas cerium accounts for nearly 30% by weight of the mineral. We therefore requested BARC to re-analyse the samples for cerium and sure enough, the levels of cerium were far higher than those of thorium (Valiathan *et al* 1989). It appeared that thorium and cerium were the indicators of monazite in the heart. These were exciting findings which suggested a role for soil elements in the causation of EMF. Indeed our report on the geo-chemical basis of EMF marked a point of departure and shifted the debate on the causative mechanism of the disease to the non-traditional context of geochemistry (Valiathan and Kartha 1990).

The geochemical basis, which we postulated as the basis for EMF, was straightforward. Magnesium is a physiological cation, which plays a crucial role in numerous biochemical reactions in the body. Children require more magnesium than adults because of the higher growth needs for the element. Poor children who subsist on rice and tuber crops like tapioca develop magnesium deficiency, which may also be enhanced by the poor absorption of magnesium in the gut due to frequent episodes of diarrhea. While severe magnesium deficiency is rare, mild and moderate deficiencies are common among poor children in Kerala and other parts of the world. One of the biological effects of magnesium deficiency is increased capillary permeability and greater transport of solutes in the gut. It is also well documented that soil and water in Kerala are low in magnesium.

In the coastal regions of Kerala, small children playing on the sand with bare feet and hands is a common sight. Monazite grains which are minute, stick to the hand easily and get ingested in small quantities in children. This had

been noted earlier during a survey of the Kerala coast by BARC scientists. They had also observed that tuber crops such as tapioca and elephant yam concentrate rare earth elements. When the children with magnesium deficiency ingest toxic elements directly through sand or indirectly through tuber crops, the elements are prone to get absorbed thanks to the increased permeability of the gut mucosa.

The geochemical hypothesis had the merit that it addressed the central issues in the clinico-epidemiological profile of EMF. The equatorial prevalence of the disease could be traced to the presence of monazite in the tropical soil, whose footprints of cerium were detectable in the heart tissues. The poverty of patients, on the other hand, found expression in magnesium deficiency which, so to say, softened the natural barriers of the mucosa to enable the entry of cerium. But the hypothesis raised a host of questions: some physico-chemical, others biomedical.

9. Geochemical basis – experimental support

As the initial excitement subsided, we were confronted by the question whether the lower concentration of magnesium and higher level of cerium were functionally coupled at all? Perhaps they were independent of each other, and we were conjuring a connection that did not exist? To settle this question, an experiment was carried out in a tuber crop – *Coleus parviflorus* – in culture. The plant model was chosen because tuber crops are consumed by patients and are reported to concentrate rare earth elements. When cerium was added to the medium which contained magnesium, the plant did take up cerium; but the uptake was twice as high when the magnesium content in the medium was halved. This confirmed that reverse changes in the levels of Mg and Ce were connected and reciprocal (Nair *et al* 1989). Then arose the question whether a lanthanide like cerium could play the role of magnesium in enzymatic reactions which form the core of life processes. An interesting study soon answered the query. Cibacron blue F3G-A is a substrate analogue of creatine kinase which is an important enzyme in muscle physiology. The enzyme cannot bind to its substrate without magnesium, which is an essential cofactor. An experiment showed that the binding would take place just as efficiently with cerium or thorium as with magnesium (Shivakumar *et al* 1989). Other crucial experiments showed that cerium acted at the transcription level in nanomolar concentration and stimulated fibroblasts in culture to produce collagen (Shivakumar *et al* 1992; Preeta and Nair 1999). These and other studies suggested that cerium could mimic magnesium and be biologically active under given conditions. The possibility of cerium occupying the slot of magnesium does not of course imply that the end result of the enzymatic reaction would be identical. Unlike magnesium, which forms reversible bonds and maintains the dynamic

conditions of the cell, cerium is likely to form irreversible bonds with biological ligands and cause the death of the cell. When the regular player is missing and his place is taken by an impostor with no music in his soul, the orchestra would produce cacophony instead of harmony.

The proof for the geochemical basis lay in the production of EMF in an animal model, which we knew would be far from easy. In our experiments, rats which were fed a magnesium deficient diet and given cerium adulterated water, showed magnesium deficiency, enhanced level of cerium, increased collagen content and fibrotic changes in the heart which are characteristic of EMF (Kumar *et al* 1996). In repeating the study in rabbits, we also observed changes in the pressure curve in the left ventricle, which are a hallmark of diastolic dysfunction or failure to relax in EMF (Kantha *et al* 1998). This was as close as one could get to the final proof in the causation of the disease. It cheered us that the geochemical basis of EMF found mention in most standard international texts of cardiology and reviews on cardiomyopathies.

Two decades after the publication of our initial reports on EMF, the prevalence of the disease has declined in Kerala. At the Chitra Institute which attracted the majority of these very sick patients, their percentage among all cardiac cases registered from 1983 – 1985 averaged 0.6% per year, which dropped to 0.2% in 2003 – 2005 even though the admission policy of the institution had not changed. Professor Sezi of Makerere University, Uganda where EMF was discovered by Professor Davies told me even in 1997 that they saw fewer patients with EMF, which he attributed to the better nutrition of poor children following the introduction of a “fish meal” scheme for children by the Ugandan Government. Better nutrition of children would correct magnesium deficiency and could account for the decreasing prevalence of EMF in Kerala as well. Our studies on EMF could claim no credit for this happy turn of events but they would suggest a possible mechanism for the prophylactic role of good nutrition in the decline of EMF.

10. In Caraka's company

To everything there is a season and a time to every purpose, said the Preacher. I laboured in the Chitra vineyard for two decades when the pickings were not bad. My long season ended in 1994 when I opted for a break with the past of several decades in cardiac surgery. The break was not only geographic and professional but also intellectual. Some years earlier, I had read the Caraka Samhita while preparing to give the Gandhi lecture at the Raman Research Institute, Bangalore, and felt that there was more in it “than met the eye”. After the lecture, Professor Satish Dhawan put his arm around my shoulder and said to me “Valiathan, I had heard Caraka's name but never knew that such ideas had been

conceived in India so long ago. You should write on the subject seriously”. The time for seeking Caraka's company came five years after my departure from the Chitra Institute, and my steps have revolved ever since among the gurukulas of Caraka, Susruta and Vagbhata (three ancient authorities of *Ayurveda*). My two studies on them were published, and a third is on the way (Valiathan 2003, 2007). In this journey to the past, I no longer fret over traffic jams because there are none; nor do I worry about overtaking or being overtaken! As I switch to the slow lane, I am not unaware that “the past is preserved by itself, automatically. In its entirety, probably, it follows us at every instant. We think only with a small part of our past, but it is with our entire past, including the original bent of our soul, that we desire, will and act” (Bergson 2005).

P C Ray regarded the centuries from 600 BC – 800 AD as the Ayurvedic period in India because Ayurveda (literally, knowledge of life) was not only the mother of life sciences but also the cradle of chemistry. After nine centuries of neglect and two of active suppression, Ayurveda had an unprecedented resurgence in India during the twentieth century. According to some estimates 70% of Indians use Ayurvedic treatment regularly or periodically. The number of Ayurvedic physicians graduating every year exceeds 12000 and their role in health care delivery is expanding rapidly. The herbal drug industry is booming. In spite of these developments, scientific studies in Ayurveda have been minimal thanks to the rigid segregation of the scientific and Ayurvedic communities in India. There has been virtually no scientific interest in Ayurveda except in herbal drugs. This has impoverished science and Ayurveda and deprived science of the opportunity to explore an uncharted land of great promise at home. Several years of textual study have persuaded me that concepts, procedures and products exist in Ayurveda, which would lend themselves to investigation by the methods of modern science. These studies would include, for example, the possible genomic basis of dosha prakritis (*three primary dosha prakritis consist of three groups of physical, behavioural and psychological traits. Fixed at the time of conception and unalterable, they determine the manifestation of disease and response to treatment in individuals*); functional genomic studies of three groups of anti-dosha plants (*groups of plants believed to counter the disorders caused by the imbalance of three doshas*); metabolic and immunologic correlates of panchakarma (*five evacuative procedures following elaborate preparation to clear the body of “toxins”; highly popular, they are claimed to have efficacy in several degenerative diseases*), the effect of rasayanas on DNA chain break repair (*procedures and drugs to promote ageing without infirmities*); and the microstructure of bhasmas (*powders prepared from metals and minerals after elaborate processing: potent and claimed to be non-toxic*). It has gratified me that established

scientists from reputed institutions and universities all across India and senior Ayurvedic physicians are taking part in these collaborative studies which form the core of "A Science Initiative in Ayurveda". These are projects in basic science, each taking a cue from traditional knowledge and each contributing strands of varied hues for the fabric of Ayurvedic Biology (Valiathan 2006).

11. Epilogue

Now the twilight has come, when the day merges into the night. I am fortunately in good health and able to travel and work hard everyday. Like Marcus Aurelius, I could fill an entire page expressing my gratitude to a great variety of individuals in three continents. I have many blessings to count, and no regrets or disappointments. Sometimes a tinge of regret does appear like a fleeting shadow that I forfeited the chance to learn Veena from my mother and gain better proficiency in Sanskrit from my teacher Rama Sastri in my school days. Recently, we had a reunion of the 1951 batch of the Trivandrum Medical College. The Grim Reaper had claimed a third of our group and some were ill. Those who came were reputed and senior physicians who had occupied high positions and enjoyed professional success in Kerala. As I sat among them, it struck me that my life and work had been cast so very differently from theirs. I left Trivandrum after graduation and spent five years in the UK and US for postgraduate training; thereafter, my serial stops of varying duration included Mumbai, Chandigarh, Baltimore, Washington DC, Delhi, Chennai, Trivandrum and Manipal. I was blown hither and thither by great winds which I could neither comprehend nor control. My nomadism was not limited to geography; it cast a spell on my mind as well. From cardiac surgery and research on EMF, I moved so deeply into biomedical engineering that I was made a Fellow by the National Academy of Engineering; the next phase saw me in the field of higher education as a Vice-Chancellor, when I had nothing to do with what I had done earlier; now, as I walk into sunset, I have gone back in time to live in the company of Caraka, Susruta and Vagbhata and develop a science initiative in Ayurveda for the 21st century. Far from grudging, I must admit that nomadism agrees with me and invigorates me with fresh doses of energy.

References

- Bergson H 2005 *Creative evolution* (New York: Cosimo) Ch. 1, p. 7
- Bhuvaneshwar G S, Ramani A V and Valiathan M S 1983 A tilting disc valve – Component materials and hydraulic function; *Bull Mater. Sci.* **3** 111–121
- Bhuvaneshwar G S, Muraleedharan C V, Ramani A V and Valiathan M S 1991a Evaluation of materials for artificial heart valves; *Bull. Mater. Sci.* **14** 1363–1374
- Bhuvaneshwar G S, Muraleedharan C V, Lal G A V, Ramani A V and Valiathan M S 1991b Synthetic Sapphire as an artificial heart valve occluder – promise and problems; *Trans. Indian Ceram. Soc.* **50** 87–92
- Bhuvaneshwar G S, Muraleedharan C V, Vijayan G A, Kumar R S and Valiathan M S 1996 Development of the Chitra Tilting disc heart valve prosthesis; *J. Heart Valve Dis.* **5** 448–458
- Gott V L, Whiffen J D and Dutton R C 1963 Heparin bonding on colloidal graphite surfaces; *Science* **142** 1297–1298
- Gott V L, Whiffen J D and Valiathan M S 1968 Graphite-Benzalkonium. Heparin coatings on plastics and metals; *Ann. NY Acad. Sci.* **146** 21–29
- Kartha C C, Eapen J T, Radhakumary C, Ramankutty V, Ramani K and Lal A V 1998 Pattern of cardiac fibrosis in rabbits periodically fed a magnesium restricted diet and administered rare earth chloride; *Biol. Trace Elem. Res.* **63** 19–30
- Kumar B P, Shivakumar K, Kartha C C and Rathnam K 1996 Magnesium deficiency and cerium promote fibrogenesis in rat heart; *Bull. Environ. Contam. Toxicol.* **57** 517–524
- Kumar R S, Bhuvaneshwar G S, Magotra R, Muralidharan S, Rajan R S, Saha D, Subba Rao K S V K, Valiathan M S, Radhakrishna S and Ramani A V 2001 Chitra heart valve: Results of a multi centric study; *J. Heart Valve Dis.* **10** 619–627
- Lalonde J B, Valiathan M S and Ballinger W F 1964 Hepatic regulation of sodium and water in ascites; *JAMA* **187** 117–118
- Nair R R, Gupta P N, Valiathan M S, Kartha C C, Eapen J T and Nair N G 1989 Enhanced cerium concentration in magnesium deficient plants; *Curr. Sci.* **58** 696–697
- Preeta R and Nair R R 1999 Stimulation of cardiac fibroblast proliferation by cerium: a superoxide anion mediated response; *J. Mol. Cell. Cardiol.* **31** 1573–1580
- Shivakumar K, Appukuttan P S and Kartha C C 1989 Interactions of thorium and cerium with adenine nucleotides; *Biochem. Int.* **19** 845–853
- Shivakumar K, Nair R R and Valiathan M S 1992 Paradoxical effect of cerium on collagen synthesis in cardiac fibroblasts; *J. Mol. Cell. Cardiol.* **24** 775–780
- Topaz S R, Ameli M M, Morovati S S, Valiathan M S, Brown B G and Gott V L 1967 Construction of a rigid case, double ventricle, artificial heart; *Trans. Am. Soc. Artif. Intern. Organs* **13** 294
- Valiathan M S, Whiffen J D, Weldon C S and Gott V L 1966 Endocardial prosthetic junction thrombosis – an experimental study of etiological factors; *Trans. Am. Soc. Artif. Intern. Organs* **12** 174–178
- Valiathan M S, Topaz S R and Ballinger W F 1967 Electrical activity of the canine liver; *J. Surg. Res.* **7** 186–187
- Valiathan M S, Weldon C S, Bender H W, Topaz S R and Gott V L 1968 Resection of aneurysms of the descending thoracic aorta using a GBH coated shunt bypass; *J. Surg. Res.* **8** 197–205
- Valiathan M S 1969 A new look at prosthetic materials – Hunterian Lecture delivered at the Royal College of Surgeons; *Ann. R. Coll. Surg.* **45** 131–149
- Valiathan M S, Kartha C C, Pandey V K, Dang M S and Sunta C M 1986 A Geochemical basis for endomyocardial fibrosis; *Cardiovasc. Res.* **20** 679–682

- Valiathan M S, Balakrishnan K G, Sankarkumar R and Kartha C C 1987 Surgical treatment of endomyocardial fibrosis; *Ann. Thorac. Surg.* **43** 68–73
- Valiathan M S, Kartha C C, Eapen J T, Dang H S and Sunta C M 1989 Rapid communication: A geo-chemical basis for endomyocardial fibrosis; *Cardiovasc. Res.* **23** 647–648
- Valiathan M S and Kartha C C 1990 Endomyocardial fibrosis: possible connection with myocardial levels of thorium, magnesium and cerium; *Int. J. Cardiol.* **28** 1–5
- Valiathan M S 2003 *The legacy of Caraka* (Hyderabad: Orient Longman)
- Valiathan M S 2006 *Towards Ayurvedic biology* (Bangalore: Vision Document. Indian Academy of Sciences)
- Valiathan M S 2007 *The legacy of Suśruta* (Hyderabad: Orient Longman)
- Whiffen J D, Young W P and Gott V L 1964 Stability of the thrombus resistant GBH surface in an anti-heparin environment; *J. Thorac. Cardiovasc. Surg.* **48** 317–322

ePublication: 5 July 2008