Special Section :
Metabolism and Neural Function - Charles Roe
(Honor Special Issue)

Guest Editor:
Juan M. Pascual
The life, times and work of Charles R. Roe, M.D.

In 1959 Charles (Charlie) R. Roe graduated from Duke University with a degree in Zoology followed by medical school at the University of Maryland for two years. Following his second medical school year in 1961, he took a leave of absence to participate in a special one-year program at Duke Medical Center created for pre-doctoral and post-doctoral medical students (six of each per year) who desired exposure to both basic and medical research. This program was designed and directed by Dr. James B. Wyngaarden (who later became head of NIH) for students of medicine that had not decided whether to choose “practice”, “research”, or a combination that was right for their future. Dr. Wyngaarden convinced Charlie to transfer to Duke Medical School for the balance of his medical school experience. Charlie received his MD degree at Duke and then because of his continuing interest in embryology, morphology and biochemistry, he chose Pediatrics for post-doctoral training in 1964.

Following internship in 1965, Charlie was accepted as a clinical associate at the NIH in the newly developing National Institute of Child Health (NICHD). Due to the absence of a fully developed intramural program at that time, he was offered (and accepted with enthusiasm) the choice of 2 years training in Biochemistry with Dr. Nathan O. Kaplan, Chairman of Biochemistry at Brandeis University in Waltham, Massachusetts and editor of the series “Methods in Enzymology”. Dr. Kaplan allowed him to pursue his prior interest in the varying substrate specificities of bacterial hydroxy-steroid dehydrogenases. This provided him with major experience in bacterial fermentation, enzyme purification/kinetics, and development of novel techniques in electrophoresis. These studies resulted in his first 2 publications [1, 2].

At Brandeis, Charlie shared a lab with Dr. Hans Eppenberger from Zurich (an expert on the evolution of creatine kinase), and Dr. Sam Nerenberg (later Chairman of Pathology at University of Illinois) who was expert in electrophoretic techniques. The departmental focus was mainly on mechanisms producing isoenzymes and organ isoenzyme profiles for lactate dehydrogenase, creatine kinase (CPK), and aldolase. At that time, it was well known in biochemical circles that creatine kinase isoenzymes had different organ specificity in animals: CK-NM = muscle, CK-MB = heart, and CK-BB = brain. Together with Dr. Nerenberg, Charlie performed a study of creatine kinase (CPK) isoenzymes by electrophoresis of serum obtained from patients with acute myocardial infarction. This evolved into the first specific diagnostic method to clearly detect acute myocardial damage during acute myocardial infarction [3].

Dr. Kaplan invited Charlie to stay at Brandeis and pursue a PhD degree in his department only 2 weeks after he had already committed to return to Duke Medical Center for residency and fellowship in Metabolic Disease. Charlie was overwhelmed and truly conflicted by this offer, but he explained to him that he had to continue his clinical training.

Following his return to Duke, he was awarded a five-year Research Career Development Award focused primarily on mutations of bacterial enzymes. This focus was changed to cardiology and surgical studies under the NHLBI. Between 1973 and 1979, Charlie was immersed in issues of cardiac injury in the context of clinical studies at Duke. A study of patients on the coronary care unit demonstrated the value of CPK isoenzyme analysis for more specific detection of cardiac damage even in the face of non-specific electrocardiographic findings [4].

The occurrence of post-operative myocardial infarction for patients undergoing coronary bypass grafting and also valve replacement was surprisingly frequent at some institutions compared to others. An intra-operative protocol was developed from anesthesia induction to discharge from the intensive care unit that involved tape recording of all surgical manipulations and timing during coronary bypass grafting and valve replacements. Blood samples for CK-MB analysis were also obtained at 15 min intervals to determine the first appearance and evolution of CK-MB relative to surgical events. This became a multi-institutional study involving the surgical and anesthesia services of Duke Medical Center, the Veterans administration Hospital of Durham, NC, New York University, University of Alabama (Birmingham), and Massachusetts General Hospital. Based on detection of increasing levels of serum CK-MB, initial cardiac injury and evolution into post-operative Infarction occurred most frequently during anesthesia induction prior to cardiopulmonary bypass. Comparisons between anesthesia management protocols at all 5 institutions revealed that some had very low incidence of post-operative infarction and others had much higher frequencies. This comparison allowed identification of possible contributing factors that could be readily modified for a subsequent study that revealed a successful reduction in post-operative intra-operative infarction [5-7]. Charlie was honored by election to Fellowship in the American College of Cardiology (FACC) for these clinical studies.

Between 1978 and 1995, as a tenured professor of Pediatrics and Director of the Division of Metabolism at Duke Medical Center, Charlie focused on improved diagnostic methods and potentially beneficial modifications of treatment for inherited biochemical dis-
orders. Recognizing the need for improved technology to enhance diagnosis and more in-depth biochemical characterization of these disorders, he was granted a 6 month sabbatical at the Medical Research Council facility in Harrow, UK to study mass spectrometry techniques and also visit other major European metabolic centers. The close relationship he had with mass spectrometry manufacturers and their developmental teams and collaborative relations with outstanding scientists provided him with unique capabilities. The first of which was the development of methods for disease-specific acylcarnitines by fast atom bombardment mass spectrometry (MS) and later electrospray-MS. This was a major improvement for diagnosis. Modification of this method by Dr. Don Chace allowed inclusion of amino acids simultaneously with acylcarnitines by a simple scanning change [8]. The improvements in detection of diagnostic analytes presented a challenge to one of his post-doctoral fellows, Dr. Naoki Kado, a Pediatrician from Kyoto, Japan. Charlie asked him if he thought it was possible during his two years to optimize quantification of acylcarnitines and amino acids from newborn screening card blood spots so that they might greatly expand metabolic screening. The entire team was thrilled when he accomplished this goal and allowed development of what is now called expanded (or supplemental) newborn screening.

During this period, Charlie recognized that the role of free carnitine was not just for transport of long-chain fatty acids into mitochondria for beta-oxidation but also contributed to intra-mitochondrial homeostasis by combating intra-mitochondrial acidosis. Associated energy deficiency had not been previously recognized in patients with beta-oxidation disorders. This changed previous concepts regarding the etiology of pathophysiology of these inborn errors. Although not proven, metabolic failure for these diseases was thought to result from accumulation of toxic intermediates generated before the enzyme block. Instead, it is now believed to be due to insufficient substrate availability for adequate function of the citric acid cycle (CAC) limiting energy production by the respiratory chain. This hypothesis stimulated the search for a dietary alternative that would provide the needed CAC substrate—an anaplerotic alternate therapy. An odd carbon triglyceride (trihexanoin) was found to be optimal for this purpose. This anaplerotic therapeutic approach was first reported in 2002 with the neuromuscular disorder very long acyl coenzyme A dehydrogenase (VLCAD) deficiency [9]. It has proven to be remarkably successful compared to conventional therapy for reduction of the clinical problems including mortality of all long-chain fatty acid oxidation disorders [10]. Recently, anaplerosis with trihexanoin has been successful with animal models of the autism spectrum disorder (Rett syndrome) [11]. Trihexanoin has also proven of benefit for the mouse model of the Glucose transporter type 1 disorder and affected humans [12,13]. It is expected that this therapeutic strategy will find extensive applications in other inherited and acquired metabolic derangements that include energy deficiency. It is hoped that since medium-chain triglyceride (MCT) oil and trihexanoin not drugs, that the availability of a food grade source will be as inexpensive as MCT oil.

In retrospect, Charlie’s career epitomizes the path followed by someone who really had difficulty deciding on the practice of medicine and a combination of basic and medical research but somehow followed both. This was easier to do between the 1960s and 1980s than it would be now—50 years later. Back then, he had the benefit of mentors and colleagues who also had combined their efforts with both basic and clinical research topics. They seemed to recognize a kindred spirit in him as a student and supported his training and career goals which, now a days, probably could not occur so freely. Charlie loved every opportunity and challenge of clinical investigation in Internal Medicine, Cardiothoracic Surgery, and Pediatrics. These studies involved many outstanding investigators as his “basic science” mentors and collaborators. For 27 years he and many others joined together on the coast of North Carolina to share current and unpublished research findings that would help them understand basic aspects of their clinical questions. The doctorate attendees’ ratio was usually PhD: MD of around 3:1 and included scientists from Europe, North and South America. Charlie was delighted to observe that many of their curriculum vitae included “Attendance at the Long Beach Institute, Oak Island, NC, USA.”

Among the many individuals who have made Charlie’s career possible, several stand out: James B Wyngaard, MD assisted him via the first training in basic science during Medical School; Jerome S. Harris, MD guided him in Pediatrics; Nathan O. Kaplan, PhD offered 2 years of basic science training in Biochemistry; James B Sidbury, MD was a supportive mentor in Pediatric Metabolism and continued research. Henri Brunengraber, PhD shared his extensive store of biochemical and clinical knowledge; Horst Schulz, PhD provided assistance as the world expert in lipid chemistry and Howard Sprecher offered expertise in organic and labeled synthesis. Charlie’s international mentors and collaborators include Cornells Jakobs, PhD and his diagnostic and research team in inherited metabolic disease; Christine Vianey-Saban PhD supplied expertise in enzymatic diagnosis; Nils Gregersen, PhD, whose career initiated with biochemical and organic chemical studies and later continued with molecular research was also very supportive. The closeness with patients and their families, which Charlie enjoyed to an immense degree, and the challenges of optimizing treatment are among the greatest stimuli that a clinical researcher may ever experience.

References