Introduction

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Our understanding of mitochondrial and electron transport chain disorders in man has progressed rapidly over the last several years. The presentations at the symposium and the papers contained in this volume document nicely some of this recent progress. We appreciate the generous support by the Brent W. Brees/Dows Metabolic Research Fund of this symposium.

Dr. Douglas Wallace of Emory University provides an overview of his studies of the maternally inherited mitochondrial DNA and the involvement of this genome and organelle in neuromuscular diseases such as Leber's hereditary optic neuropathy and the syndrome of myoclonic epilepsy and ragged red fibers (MERRF). His innovative work has produced a variety of molecular techniques to screen for both point mutations and deletions in mitochondrial DNA. Dr. Wallace's pioneering studies of the mitochondrial genome and its involvement and role in human evolution and pathology add an unique dimension to his contribution.

Dr. Nancy Kennaway from Oregon summarizes her work and that of her collaborators in studying mitochondrial myopathies and cardiomyopathies associated with complex III and IV deficiencies. She also discusses the as yet incompletely understood questions of clinical and biochemical heterogeneity and tissue-specific expression of mitochondrial polypeptides in these disorders.

Dr. Salvatore DiMauro of Columbia, whose contributions in the area of electron transport disorders and neuromuscular disease have been both seminal and wide-ranging, discusses cytochrome c oxidase deficiency in man, its biochemistry and molecular genetics. His wide experience and large patient population enhance his discussion of the clinical, enzymatic, and molecular heterogeneity in this disorder.

Dr. Orest Hurko of Johns Hopkins summarizes his incisive studies of the clinical and molecular pathology of disorders in the family of chronic progressive external ophthalmoplegias. His precise studies of clinical and biochemical variation and variable tissue heteroplasmy of mitochondrial DNA deletions are of interest and relevance to us all.

Dr. Brian Robinson of Toronto, an internationally renowned expert in the study of pyruvate and lactate metabolism in man and the lactic acidemias, discusses approaches, techniques, and the conclusions he has developed in studying respiratory complex defects expressed in diploid fibroblasts.

Throughout these talks, several themes recur. These authors and the other investigators engaged in the field are continually striving to refine correlation between clinical phenotype and biochemical defects in these disorders, as well as integrate the recent advancements and information derived from molecular and genetic studies into their approaches and conclusions. The marked overlap of clinical and biochemical phenotypes and syndromes, the variation noted in many of these disorders through time, and the difficulty in assigning some cases to any recognized syndrome of mitochondrial dysfunction are compounded by the difficulty in precisely correlating clinical phenotypes with the biochemical and molecular defects. As our understanding progresses, we hope to better understand the differences in clinical and biochemical phenotypes produced by point mutations *versus* deletions in the mitochondrial genome, as well as envision the phenotypes associated with as yet unrecognized defects in mitochondrial DNA.

Although much attention has been focused on these recently identified defects in the maternally inherited mitochondrial genome, it is good to remember that more than three quarters of the gene products and polypeptides involved in mitochondrial electron transport chain function are encoded in the nuclear genome. In addition, all other mitochondrial polypeptides, including almost all those involved in the tricarboxylic acid cycle, the various membrane transporters, and the transcription and translation machinery of the mitochondrion are also encoded in the nuclear DNA. Further molecular and clinical studies will likely identify mitochondrial disorders in man associated with defects in these nuclear-encoded mitochondrial functions. In addition, the existence of certain disorders that evolve through time, such as the reversible complex IV (cytochrome c oxidase) deficiency identified by DiMauro and coworkers, suggest that developmental switching and tissue-specific expression of nuclear-encoded isoforms will surely be important in understanding these disorders.

In sum, although a great deal has been learned, a great deal remains unknown. The study of mitochondrial disorders in man should present new and unique opportunities and vistas for study and analysis over the next decades. Important clinical, biochemical, genetic, and evolutionary insights should be gained as a result of these studies.