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MITOCHONDRIAL MEDICINE

A history of mitochondrial diseases

Salvatore DiMauro

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Abstract This articles reviews the development of mitochondrial medicine from the premolecular era (1962–1988), when mitochondrial diseases were defined on the basis of clinical examination, muscle biopsy, and biochemical criteria, through the molecular era, when the full complexity of these disorders became evident. In a chronological order, I have followed the introduction of new pathogenic concepts that have shaped a rational genetic classification of these clinically heterogeneous disorders. Thus, mitochondrial DNA (mtDNA)-related diseases can be divided into two main groups: those that impair mitochondrial protein synthesis in toto, and those that affect specific respiratory chain proteins. Mutations in nuclear DNA can affect components of respiratory chain complexes (direct hits) or assembly proteins (indirect hits), but they can also impair mtDNA integrity (multiple mtDNA mutations), replication (mtDNA depletion), or mtDNA translation. Besides these disorders that affect the respiratory chain directly, defects in other mitochondrial functions may also affect oxidative phosphorylation, including problems in mitochondrial protein import, alterations of the inner mitochondrial membrane lipid composition, and defects of mitochondrial dynamics. The enormous and still ongoing progress in our understanding of mitochondrial medicine was made possible by the intense collaboration of an international cadre of "mitochondriacs." Having published my first paper on a patient with mitochondrial myopathy 37 years ago (DiMauro et al., 1973), I feel qualified to write a history of the mitochondrial diseases, a fascinating, still evolving, and continuously puzzling area of medicine. In each section, I follow a chronological order of the salient discoveries and I show only the portraits of distinguished deceased mitochondriacs and those whose names became eponyms of mitochondrial diseases.

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S. DiMauro (✉)
Department of Neurology, Columbia University Medical Center,
Room 4-424B College of Physicians & Surgeons,
630 West 168th Street,
New York, NY 10032, USA
e-mail: sd12@columbia.edu

The premolecular era

Old as my interest in mitochondrial medicine is, the concept of mitochondrial disease is even older. It was introduced in 1962, when a group of investigators at the Karolinska University in Stockholm, including the endocrinologist Rolf Luft (Fig. 1), the biochemist Lars Ernster, and the morphologist Björn Afzelius, described a young Swedish woman with severe hypermetabolism not due to thyroid dysfunction (Luft et al. 1962). This classical piece of translational investigation was based on three sets of data: morphological evidence of abnormal mitochondria in muscle; biochemical documentation of "loose coupling" of oxidation and phosphorylation in isolated muscle mitochondria; and excellent correlation between biochemical abnormalities (loose coupling) and clinical features (uncontrolled muscle metabolism).

Notably, this paper introduced not only the concept of mitochondrial medicine but also that of "organellar medicine," because the classical paper by Henry-Géry Hers on inborn lysosomal diseases was not published until 3 years later (Hers 1965). In another twist of history, the groundbreaking Luft disease is also the rarest of all mitochondrial disorders, having been confirmed only in one other patient, about

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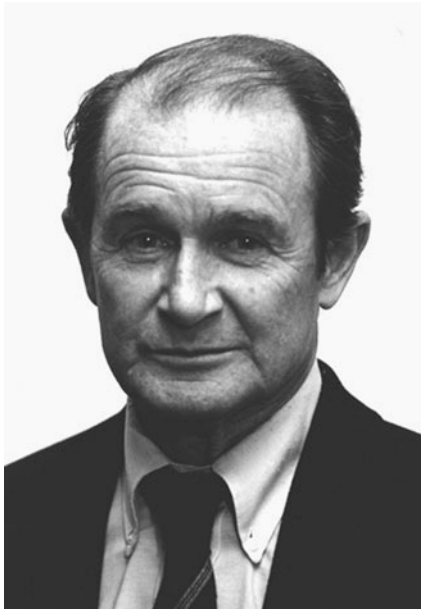

Fig. 1 Rolf Luft (1914–2007)

10 years after Luft's report (DiMauro et al. 1976; Haydar et al. 1971). A third curious feature of Luft disease is that its molecular basis remains unknown. Undoubtedly, the scarcity of patients and the lack of postmortem tissues from either one of the two patients are obstacles, but they do not completely explain our ignorance, because fibroblast cell lines from the second patient are available and we, among others, have screened numerous attractive candidate genes to no avail. In the decade that followed Luft's report, the attention of clinical scientists was largely directed to muscle disorders and muscle morphology. At the University of Pennsylvania, neurologist G. Milton Shy (Fig. 2) and neuropathologist Nicholas Gonatas conducted systematic ultrastructural investigations of muscle biopsies (Shy and Gonatas 1964; Shy and Gonatas 1966) and gave fanciful Greek names to myopathies with too many normal-looking mitochondria (pleoconial myopathy) or with greatly enlarged mitochondria (megaconial myopathy). In fact, Shy and Gonatas may have foretold the importance of mitochondrial DNA (mtDNA) in 1965 when, in a review article, they stated "If mitochondria are self-replicating organelles as recent chemical and morphological evidence has suggested, these two myopathies [pleoconial and megaconial] may be due to a defective gene"—by implication, a mitochondrial gene (Gonatas and Shy 1965).

In 1963, W. King Engel, then at the National Institutes of Health (NIH), introduced a simple histochemical assay—a modification of the Gomori trichrome stain (Engel and Cunningham 1963)—that allowed for the detection of abnormal mitochondrial proliferation in muscle as irregular purplish patches in fibers that were dubbed "ragged-red" (RRF). Biochemical studies were not conducted systematically until the 1970s and were often inconclusive due to the difficulty of isolating functionally intact mitochondria from human muscle biopsies and to the relative insensitivity of polarography (the predominant biochemical technique then employed) in detecting partial metabolic blocks. However, the application of specific biochemical assays led to the description of increasing numbers of metabolic defects, including deficiencies of pyruvate dehydrogenase complex (PDHC) (Blass et al. 1970), palmitoylcarnitine transferase (CPT) (DiMauro and DiMauro-Melis 1973), and carnitine (Engel and Angelini 1973; Karpati et al. 1975), as well as defects of individual complexes of the respiratory chain, including complex III (Spiro et al. 1970) and complex IV (Willems et al. 1977).

In 1985, we proposed a general biochemical classification of the mitochondrial diseases based on the five main steps of mitochondrial metabolism: defects of substrate transport (e.g., CPT deficiency); defects of substrate utilization (e.g., PDHC deficiency); defects of the Krebs cycle (e.g., fumarase deficiency); defects of the electron-transport chain [e.g., cytochrome *c* oxidase (COX) deficiency]; and defects of oxidation/phosphorylation coupling (e.g., Luft's disease) (DiMauro et al. 1985). Whereas this classification system remains valid and each category has been greatly enriched with new specific entities, it has also become increasingly accepted that the term "mitochondrial encephalomyopathies," introduced in 1977 by Yehuda Shapira to acknowledge the often multisystemic nature of these disorders (Shapira et al. 1977), be reserved for diseases due to defects in the respiratory chain. This conventional wisdom is supported by the biochemical complexity of the mitochondrial respiratory chain, by its unique dual genetic control, and by the extraordinary clinical and genetic heterogeneity of the diseases related to its dysfunction.

Fig. 2 G. Milton Shy (1919–1967)

The multisystemic nature of most mitochondrial diseases generated controversy between "splitters," who found it both useful and rational to identify distinct syndromes (Rowland 1994), and "lumpers," who stressed overlapping features and considered individual clinical pictures simply as variations on a common theme (Petty et al. 1986). In retrospect, the truth, as usual, seems to sit in the middle. To the credit of the splitters (who probably deserve most of the credit), there are several well-defined and easily recognizable syndromes identified by less easily pronounceable acronyms, such as MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes) (Pavlakis et al. 1984), MERRF (myoclonus epilepsy with RRF) (Fukuhara et al. 1980), and myo-, neuro-, gastrointestinal encephalopathy (MNGIE) (Bardosi et al. 1987). To the credit of the lumpers, there are many examples of overlap syndromes, although these seem to be more the exception than the rule.

The molecular era

Defects of the respiratory chain

The mtDNA: a Pandora's box

The "big divide" in the history of mitochondrial diseases, and the beginning of the molecular age, was the description, in 1988, of the first pathogenic mutations in mtDNA. Although mtDNA had been known since 1963 (Nass and Nass 1963a; Nass and Nass 1963b), clinical scientists had paid little attention to this genetic "relic" until Anita Harding (Fig. 3) and coworkers identified

Fig. 3 Anita Harding (1952–1995)

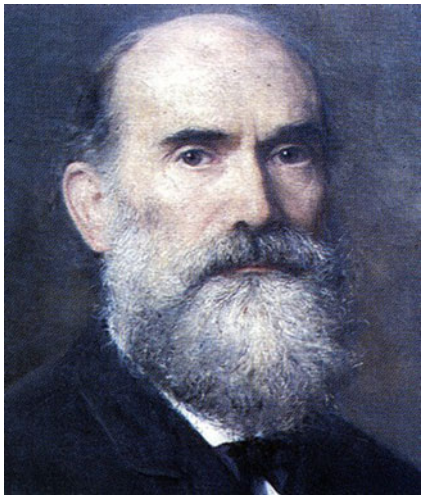

Fig. 4 Theodor Karl Gustav von Leber (1840–1917)

large-scale single deletions of mtDNA in patients with mitochondrial myopathies (Holt et al. 1988). Soon thereafter, Doug Wallace and coworkers described a point mutation in the gene encoding subunit 4 of complex I (ND4) in a family with Leber (Fig. 4) hereditary optic neuropathy (LHON) (Wallace et al. 1988).

Within a year of these discoveries, a postdoctoral fellow, Massimo Zeviani, and a graduate student, Carlos Moraes, at Columbia University Medical Center (CUMC), as well as Lestienne and Ponsot in France (Lestienne and Ponsot 1988), showed that large-scale rearrangements were associated with various forms of progressive external ophthalmoplegia (PEO), including the Kearns-Sayre (Fig. 5) syndrome (KSS) (Moraes et al. 1989; Zeviani et al. 1988). In 1990, John Shoffner in Doug Wallace's lab identified a point mutation in transfer RNA ($tRNA^{Lys}$) in patients with the MERRF syndrome (Shoffner et al. 1990), and Yu-ichi Goto identified a point mutation in $tRNA^{Leu(UUR)}$ in patients with MELAS (Goto et al. 1990), thus providing molecular support to the point of view of the splitters.

In the next decade, new pathogenic mutations of mtDNA were described at the pace of about ten per year, such that 115 point mutations were listed in the 1 January 2001 catalogue of *Neuromuscular Disorders* (Servidei 2001). To these must be added innumerable mtDNA rearrangements (deletions, duplications, or both together). The tempo at which pathogenic mtDNA mutations are discovered has not abated, because by 2006, more than 200 changes were listed in the Appendix to the textbook *Mitochondrial Medicine* (DiMauro et al. 2006).

Although mtDNA-related disorders were considered rare, several epidemiological studies conducted at the beginning of the new millennium in children and adults by the Swedish group of Mar Tulinius (Darin et al. 2001), the Australian group of David Thorburn (Skladal et al.

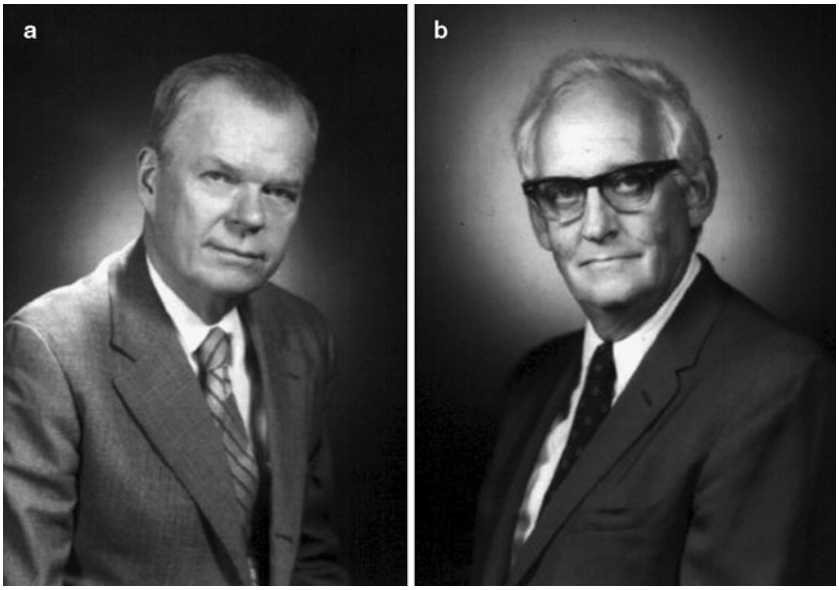

Fig. 5 Thomas P. Kearns (ophthalmologist, 1922–) and George P. Sayer (pathologist, 1911–1992)

2003) and the British group of Doug Turnbull and Patrick Chinnery (Schaefer et al. 2007; Schaefer et al. 2004) came to the remarkably similar conclusion that the overall prevalence of mtDNA diseases was about 1 in 5,000, higher than we had thought. Then, in 2008, the group of Patrick Chinnery in Newcastle (UK) screened mtDNA for ten pathogenic point mutations from more than 3,000 cord bloods of normal newborns and came up with the unexpected finding that at least 1 in 200 individuals harbor pathogenic mtDNA mutations (Elliott et al. 2008). When one considers only the typical MELAS mutation, m.3243A > G, the prevalence was 1 in 750, similar to that (1 in 423) encountered by Carolyn Sue's group in Sydney, Australia (Manwaring et al. 2007). As the frequency of typical MELAS is obviously much lower, the mutations must be present in subthreshold amounts in many asymptomatic individuals, but it could also surpass the pathologic threshold in individual tissues in patients with diseases other than MELAS, such as diabetes mellitus (Kadowaki et al. 1994).

Whereas the small circle of mtDNA was becoming saturated with mutations, increasing numbers of mitochondrial patients had family histories compatible with Mendelian genetics. The time had come for clinical scientists to direct their attention to the nucleus. Before recounting this story, however, I wish to acknowledge the efforts of many scientists to understand the pathogenesis of mtDNA mutations.

Pathogenesis of mtDNA mutations: still terra incognita

The rules of mitochondrial genetics—maternal inheritance, heteroplasmy/threshold effect, and mitotic segregation—go a long way in explaining many of the peculiarities of mtDNA-related disorders. Thus, maternal inheritance is an important clue to the diagnosis of mtDNA-related disorders. To be sure, there was one partial exception to this rule: in 2002, Marianne Schwartz and John Vissing reported a sporadic patient with mitochondrial myopathy and a microdeletion in ND2 who had inherited most of his muscle mtDNA (but not the deletion nor the mtDNA in other tissues) from his father (Schwartz and Vissing 2002). This "cause célebre" was rapidly deflated when several groups, including that of Vissing, showed that the myopathic patient with paternal mtDNA was the classical exception that confirmed the maternal inheritance rule (Filosto et al. 2003; Schwartz and Vissing 2004; Taylor et al. 2003b). However, this freak case was living proof that mtDNA molecules can recombine (Kraytsberg et al. 2004).

Heteroplasmy and the threshold effect are crucial concepts by which to understand the extraordinary clinical heterogeneity of mtDNA-related diseases. Usually, pathogenic mutations are heteroplasmic, and the pathogenic threshold in most tissues is both high and steep, as exemplified by the most common MELAS mutation, m.3243A > G. There is also a good correlation between mutation load and severity of clinical features, best shown by the neuropathy, ataxia, and retinitis pigmentosa/maternally inherited Leigh (Fig. 6) (NARP/MILS) mutation, m.8993 T > G: when the mutation load is around 70–80%, patients are adults with NARP; whereas when the mutation load is around 90%, patients are infants or children with MILS syndrome (Holt et al. 1990; Tatuch et al. 1992).

As mtDNA mutates spontaneously at a high rate, and most changes are neutral polymorphisms—a situation exploited in anthropology and forensic medicine—a set of conventional rules was established to prove the pathoge-

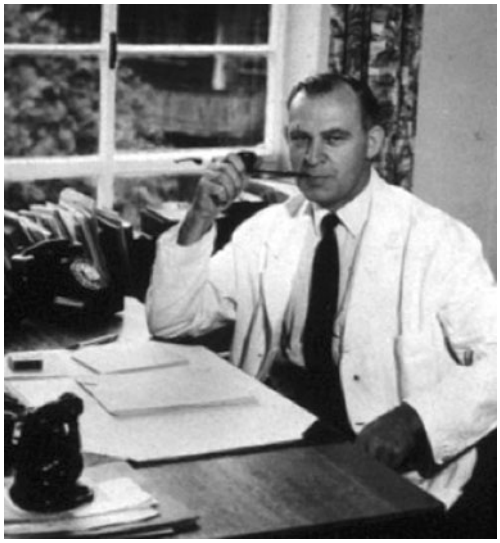

Fig. 6 Denis A. Leigh (1915–1998)

nicity of a novel mtDNA mutation. First, the mutation should not be found in normal individuals of the same ethnic group. Second, it should alter a site conserved in evolution that is, by implication, functionally important. Third, it should cause single or multiple respiratory chain enzyme deficiencies in affected tissues. Fourth, there should be a correlation between mutant load and clinical severity. A useful and relatively simple stratagem introduced by Carlos Moraes (Moraes et al. 1992) to correlate degree of heteroplasmy and function is single-fiber polymerase chain reaction (PCR)—that is, PCR performed in individual fibers "plucked" from a thick cross section of skeletal muscle stained with the modified Gomori or the COX histochemical reaction followed by quantitation of the mutation load by restriction fragment-length polymorphism (RFLP) analysis. This technique has consistently demonstrated that heteroplasmic pathogenic mutations are more abundant in RRF than in non-RRF and in COX-negative than in COX-positive fibers. Another simple "trick" that proved extremely useful diagnostically was introduced by Eduardo Bonilla (Fig. 7), who noted that when the succinate dehydrogenase (SDH) and COX stains are superimposed on the same muscle section, the brownish COX stain prevails in normal fibers, whereas the normally obscured bluish SDH stains shines through in COX-negative or even COX-deficient fibers (Bonilla et al. 1992; Tanji and Bonilla 2001).

The concept of heteroplasmy, and especially the observation that mtDNA sequence variants segregate rapidly from one generation to the next and among siblings of the same mother, has led to the concept of a genetic bottleneck for the transmission of mtDNA, whose mechanism, however, remains controversial. The predominant view had been that the bottleneck occurs during embryonic

Fig. 7 Dr. Eduardo Bonilla

development and is due to a marked reduction in germline mtDNA copy number (Cree et al. 2008; Jenuth et al. 1996). However, this view has been challenged by recent evidence from collaborative work of Hayashi and Yonekawa showing that the bottleneck is not accompanied by a reduction in germline mtDNA content (Cao et al. 2009), and by data from Eric Shoubridge's lab documenting that the genetic bottleneck does not occur during embryonic oögenesis but rather during postnatal folliculogenesis (Wai et al. 2010). It is clear that the controversy is not over, and the explanation may not be univocal.

A second puzzle regards how heteroplasmy (or, in fact, homoplasmy) develops in somatic tissues. These variations could be the result of stochastic processes in early embryos or the result of changes occurring in adult somatic tissues, as suggested by studies of the Newcastle (UK) group in colonic crypts (Greaves et al. 2006).

One major obstacle to studying the functional consequences of mtDNA mutations is the lack of animal models due to our inability to introduce mtDNA into mitochondria of mammalian cells in a stable and heritable manner. In 1989, in the wake of pioneer work on respiration-deficient Chinese hamster cells (DeFrancesco et al. 1976; Scheffler 1986) and of rho^0 chicken cells (Dejardins et al. 1985; Morais et al. 1988), Giuseppe Attardi (Fig. 8) and Michael King (King and Attardi 1989) introduced an ingenious alternative approach based on cybrid (cytoplasmic hybrid) cells; that is, established human cell lines first depleted of

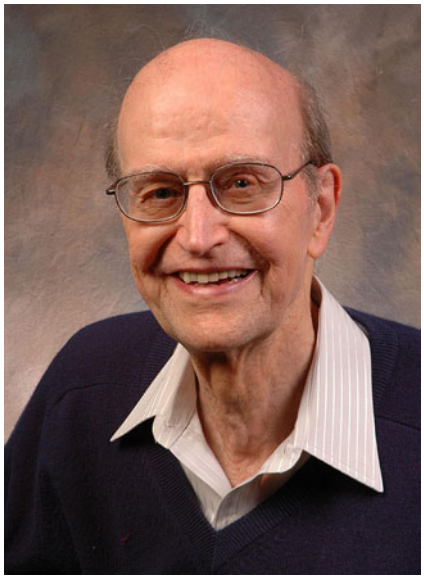

Fig. 8 Giuseppe Attardi (1923–2008)

their own mtDNA then repopulated with various proportions of mutated genomes. This technique has confirmed that single deletions and pathogenic tRNA gene mutations impair respiration, protein synthesis, and adenosine triphosphate (ATP) production and has allowed us to establish that the pathogenic threshold for most mutations is, indeed, both high and steep (Chomyn et al. 2000; King et al. 1992; Masucci et al. 1995). However, these data cannot be extrapolated to the in vivo situation, as shown by oligosymptomatic carriers of the m. 3243A > G mutation, who had abnormal ^{31}P-magnetic resonance spectroscopy (MRS) signals in muscle (Chinnery et al. 2000) and abnormal lactate peaks in both cerebrospinal fluid and brain parenchyma by ^{1}H-MRS (Dubeau et al. 2000; Kaufmann et al. 2004). The high pathogenic threshold implies a recessive quality of mtDNA mutations (to borrow a Mendelian term), but we should not forget that occasional mutations behave as dominant traits in that they are pathogenic at low levels of heteroplasmy (Sacconi et al. 2008).

More importantly, we have certainly exaggerated the role of heteroplasmy as a pathogenic requisite of mtDNA mutations, apparently forgetting that the first disease-related mutation was, in fact, homoplasmic (Wallace et al. 1988), as have been most mutations associated with LHON (Carelli et al. 2006). It is also becoming increasingly clear that homoplasmic pathogenic mutations are often tissue specific (Prezant et al. 1993; Sue et al. 1999; Taylor et al. 2003a) and even developmentally regulated, as in the reversible infantile COX deficiency (Horvath et al. 2009). These findings have given new impetus to research on modifier nuclear genes that were often mentioned perfunctorily in early papers on mtDNA-related diseases. For example, two loci on the X-chromosome may relate to the long-known prevalence of affected men in LHON (Hudson et al. 2005; Shankar et al. 2008). Also, a mutation in the nuclear gene *TRMU*, which encodes a mitochondrial protein important for tRNA modification, facilitates the expression of the deafness-associated mtDNA 12 S ribosomal RNA (rRNA) mutations (Guan et al. 2006).

In their migration out of Africa, human beings accumulated distinctive variations from the mtDNA of our ancestral "mitochondrial Eve," resulting in numerous haplotypes characteristic of different ethnic groups (Wallace 2005). It has been suggested that different mtDNA haplogroups or subhaplogroups may modulate oxidative phosphorylation, thus influencing the overall physiology of individuals and predisposing them to–or protecting them from–certain diseases (Wallace 2005). A good example of the pathogenic importance of the mitochondrial genetic background comes from studies of LHON, which have established that the risk of visual loss is greater when patients harboring each of the three major mutations belong to specific haplogroups (Hudson et al. 2007).

Twenty-two years after the discovery of pathogenic mutations in mtDNA, we have very little understanding of how the different molecular defects cause different syndromes. In fact, it is surprising that mtDNA mutations should cause different syndromes in the first place. If, as conventional wisdom dictates, mtDNA rearrangements and tRNA gene mutations impair protein synthesis and ATP production, the clinical outcome should be a swamp of ill-defined and overlapping syndromes, whereas most mutations result in well-defined and rather stereotypical presentations. It is likely that the current interest in nuclear modifier genes will reveal an unsuspected degree of indirect control of the nuclear over the mitochondrial genome. For now, however, let us resume the history of how alterations of the direct nuclear control were discovered.

Mutations of nuclear DNA: multiple deletions and depletion of mtDNA

In 1989 and in 1991, two new types of Mendelian mitochondrial disorders were identified by Massimo Zeviani and Carlos Moraes, then working separately. Zeviani, who had returned to Italy and was working at the National Neurological Institute "Carlo Besta" in Milan, described some Italian families with autosomal dominantly inherited PEO and multiple mtDNA deletions in muscle, the first example of a group of mitochondrial disorders apparently due to faulty communication between nuclear and mitochondrial genomes (Zeviani et al. 1989). In 1991, Moraes, still working at CUMC in New York, documented the first quantitative defect of mtDNA, mtDNA depletion, in patients with autosomal recessive disorders affecting muscle or liver (Moraes et al. 1991). In these situations, a

primary nuclear defect clearly impaired mtDNA integrity in the case of multiple mtDNA deletions, or mtDNA abundance in the case of mtDNA depletion. But which were the responsible genes?

In quick succession, three genes were associated with autosomal dominant PEO (adPEO). In 2000, a collaborative work between Anu Suomalainen at the University of Helsinki and Zeviani led to the identification of mutations in the gene (*ANT1*) encoding the adenine nucleotide translocator (Kaukonen et al. 2000); the following year, another European collaboration led by Johannes Spelbrink discovered mutations in the *PEO1* gene that encodes the Twinkle helicase (Spelbrink et al. 2001), and Gert Van Goethem in Belgium described mutations in the gene (*POLG*) encoding the one and only mtDNA polymerase (Van Goethem et al. 2001). In the years that followed, numerous clinical variants were associated with mutations in these genes, most notably, autosomal recessive forms of PEO, alone or together with sensory ataxic neuropathy, in patients with *POLG* mutations (Hakonen et al. 2005; Horvath et al. 2006; Tzoulis et al. 2006).

The first molecular causes of mtDNA depletion were discovered in Israel, when Orly Elpeleg, together with Ann Saada and Hanna Mandel, identified that mutations in the thymidine kinase 2 gene (*TK2*) are responsible for the myopathic syndrome (Saada et al. 2001) and that mutations in the deoxyguanosine kinase (*DGUOK*) gene are responsible for one of the hepatocerebral syndromes. Bob Naviaux recognized that certain mutations in *POLG* caused autosomal recessive mtDNA depletion and were associated with the most common hepatocerebral disorder of childhood, Alpers (Fig. 9) syndrome (Naviaux and Nguyen 2004; Naviaux et al. 1999).

Fig. 9 Bernard J. Alpers (1900–1981)

Michio Hirano at CUMC carried the research on MNGIE full circle, from characterizing the clinical presentation (Hirano et al. 1994) to mapping the locus to chromosome 22q (Hirano et al. 1998), to identifying the mutant gene (*TYMP*, encoding thymidine phosphorylase) in collaboration with Ichizo Nishino (Nishino et al. 1999), to defining biochemical abnormalities and mtDNA instability (Marti et al. 2003; Nishigaki et al. 2003; Spinazzola et al. 2002), to developing an effective stem cell therapy (Hirano et al. 2006).

To date, nine nuclear genes have been associated with mtDNA depletion syndromes, *TK2*, *DGUOK*, *POLG*, *SUCLA2*, *SUCLG*, *PEO1*, *RRM2B*, *TYMP* and *MPV17* (Poulton et al. 2009; Rotig and Poulton 2009; Spinazzola et al. 2009). Except for MPV17, all of the proteins encoded by these genes are involved in the homeostasis of the mitochondrial nucleoside/nucleotide pool, which explains why tampering with them would result in alterations of mtDNA maintenance (multiple deletions or depletion of mtDNA) (Spinazzola and Zeviani 2005). The only mutant protein with a different, but not yet fully defined, function is MPV17, which resides in the inner mitochondrial membrane (IMM). Interestingly, although mutations in *MPV17* have been associated with a hepatocerebral syndrome, one homozygous mutation underlies an inherited variant endemic in the Navajo population: Navajo neurohepatopathy (NNH) (Karadimas et al. 2006).

Mutations in nuclear DNA: direct hits

These mutations affect genes that encode subunits of the respiratory chain complexes. As complex II is small and entirely made up of nuclear-encoded subunits, it seems logical that the first such defect was identified in two sisters with complex II deficiency (Bourgeron et al. 1995). The time was 1995, the two girls had Leigh syndrome (LS), and the work came from Arnold Munnich's group in Paris. It took 4 more years before the Nijmegen group, founded by Rob Sengers (Fig. 10) and now led by Jan Smeitink, identified, in rapid sequence, several pathogenic mutations in highly conserved genes of complex I, mostly in patients with the clinical phenotype of LS (Smeitink and van den Heuvel 1999). Other assembly genes for complex I were identified by Denise Kirby (Fig. 11) in David Thorburn's laboratory (Kirby et al. 2004).

The first direct hit affecting complex III was reported in 2003 by the Paris group of Jean Marie Saudubray and Pierre Rustin: this deletion in the *UQCRB* gene severely alters the structure of the QP-C subunit (subunit VII) and decreases cytochrome *b* content (Haut et al. 2003). Nuclear direct hits causing LS and COX deficiency must be rare, because the first such mutation was discovered only 2 years ago, by the Zeviani group (Massa et al. 2008).

Fig. 10 Rob Sengers (1939–2006)

Primary or secondary coenzyme Q_{10} (CoQ_{10}) deficiencies can be considered direct hits. They cause five major syndromes: (i) a predominantly myopathic disorder with recurrent myoglobinuria but also central nervous system (CNS) involvement (seizures, ataxia, mental retardation) (Ogasahara et al. 1989; Sobreira et al. 1997); (ii) a predominantly encephalopathic disorder with ataxia and cerebellar atrophy (Gironi et al. 2004; Lamperti et al. 2003; Musumeci et al. 2001); (iii) an isolated myopathy, with RRF and lipid storage (Aure′ et al., 2004; Lalani et al. 2005); (iv) a generalized mitochondrial encephalomyopathy, usually with onset in infancy (Lopez et al. 2006; Mollet et al. 2007; Quinzii et al. 2006; Rotig et al. 2000; Salviati et al. 2005; Van Maldergem et al. 2002); and (v) nephropathy alone or associated with encephalopathy (Diomedi-Camassei et al. 2007). Examples of secondary CoQ_{10} deficiency include ataxia oculomotor apraxia (AOA1) associated with mutations in the aprataxin (*APTX*) gene (Quinzii et al. 2005), and the myopathic presentation of glutaric aciduria type II (GA II) due to mutations in the electron transfer flavoprotein dehydrogenase (*EFTDH*) gene (Gempel et al. 2007). The concept that primary CoQ10 deficiency was due to mutations in biosynthetic genes, first postulated by Agnes Rötig and Arnold Munnich (Rotig et al. 2000) and by the CUMC group (Musumeci et al. 2001), was validated by Michio Hirano's group with the discovery of mutations in *COQ1 (PDSS2*) (Lopez et al. 2006) and *COQ2* (Quinzii et al. 2006) and confirmed by Rötig's group with the report of mutations in *PDSS1* and *COQ2* (Mollet et al. 2007). Two papers from France and New York added to this rapidly expanding list mutations in *CABC1/ADCK3* (Lagier-Tourenne et al. 2008; Mollet et al. 2008), and a paper from the United Kingdom added mutations in *COQ9* (Duncan et al. 2009).

Fig. 11 Denise Kirby (1953–2010)

Mutations in nuclear genes: indirect hits

These mutations do not affect respiratory chain complexes directly but rather interfere with their assembly in what I have called a "murder by proxy" mechanism. This field opened up with the description of mutations in the *SURF1* gene by the groups of Eric Shoubridge at the Montreal Neurological Institute (Zhu et al. 1998) and Massimo Zeviani at the "Besta" Neurological Institute (Tiranti et al. 1998). Although mutations in the *SURF1* gene are the most common causes of COX-deficient LS, they clearly did not explain all cases, and, in short order, genetic defects were reported in other COX-assembly genes. Eric Schon and coworkers at CUMC described mutations in *SCO2*, a gene presumably involved in the transport of copper into the holoenzyme (Papadopoulou et al. 1999), and the following, year two papers from the Munnich/Rötig group reported mutations in *SCO1* and in *COX10* (Valnot et al. 2000a; Valnot et al. 2000b). After mutations in one more COX-assembly gene (*COX15*) were added by Shoubridge's group (Antonicka et al. 2003), a more complex mechanism involving a problem with mtDNA transcript processing (see next section) emerged when the molecular defect underlying the French Canadian type of Leigh syndrome (LSFC) was ascribed to mutations in the *LRPPRC* gene (encoding the leucine-rich pentatricopeptide repeat cassette protein), in a collaboration between Brian Robinson in Toronto and Vamsi Mootha in Boston (Mootha et al. 2003). This paper introduced to mitochondrial research the methodology of integrative genomics based on bioinformatics-generated intersection of DNA, messenger RNA (mRNA), and protein data sets.

Integrative genomics also facilitated identification of the *ETHE1* gene, which is responsible for ethylmalonic encephalomyopathy (EE), a devastating early-onset encephalopathy with microangiopathy, chronic diarrhea, and

massively increased levels of ethylmalonic acid and short-chain acylcarnitines in body fluids (Tiranti et al. 2004). The story of EE has been developed by Valeria Tiranti and Massimo Zeviani from the discovery of the gene to the demonstration that ETHE1 is a mitochondrial matrix thioesterase (Tiranti et al. 2006) and to the creation of *Ethe1*-null mice, which allowed them to document that thiosulfate and sulfide accumulate excessively both in the animal models and in patients due to the lack of sulfur dioxygenase activity (Tiranti et al. 2009). Because sulfide is a powerful COX inhibitor, they ended up describing an indirect hit of a different kind and very possibly a prototype of other such pathogenic mechanisms.

Indirect hits affecting complex III thus far involve a single protein, BCS1L, a member of the AAA family of ATPases needed for insertion of the Rieske FeS subunit into the complex. Different mutations, however, cause very different syndromes—from the rapidly fatal and multi-systemic growth retardation, aminoaciduria, cholestasis, iron overload, lactic acidosis, and early death (GRACILE) initially defined through a mostly Finnish/British collaboration including Leena Peltonen, Anu Suomalainen, and Doug Turnbull (Visapaa et al. 2002), to the much more benign Björnstad syndrome (sensorineural hearing loss and pili torti) (Hinson et al. 2007).

The first molecular defect involving complex V (ATP synthase) was, in fact, an indirect hit, a homozygous missense mutation in the *ATP12* (now called *ATPAF2)* assembly gene reported from Belgium by Linda De Meirleir and Rudy Van Coster in an infant who died at 14 months (De Meirleir et al. 2004). A collaboration of the Czech group led by Josef Houstek with a number of colleagues from Austria, Belgium, and Sweden identified 14 patients with Mendelian defects of complex V documented by blue native electrophoresis and Western blotting (Sperl et al. 2006). Whole-genome homozygosity mapping, gene-expression analysis, and DNA sequencing by the Czech group in 25 infants of Roma ethnic origin with severe multisystem symptoms, lactic acidosis, and 3-methylglutaconic aciduria revealed a homozygous mutation in the *TMEM70* assembly gene in 23 patients and a compound heterozygous mutation in the same gene in one patient (Cizkova et al. 2009).

The first indirect hit involving complex I was discovered in 2005 by the Shoubridge group, and it affected a gene called *NDUFA12L* (now known also as *B17.2 L* or mimitin) (Ogilvie et al. 2005)

Curiously, the first complex in which direct hits were identified, complex II, was the last complex in which a defective assembly factor, an LYR-motif protein encoded by the *SDHAF1* gene, was found in children with psychomotor regression and leukoencephalopathy in a Milan–Munich collaboration (Ghezzi et al. 2009).

Defects of mitochondrial translation

This is—for now, at least—the last frontier in the field of respiratory chain defects. As pediatric neurologists encountered increasing numbers of patients with multiple respiratory chain defects but no mtDNA tRNA mutations and no evidence of mtDNA depletion, they directed their attention to the complex nuclear-encoded apparatus needed for mtDNA translation. In 2004, three groups described three distinct gene defects. Orly Elpeleg reported a homozygous nonsense mutation in the *MRPS16* gene, which controls the transcription of the 12 S rRNA, in an infant with neonatal lactic acidosis, dysmorphism, and agenesis of the corpus callosum (Miller et al. 2004). A joint effort from Jan Smeitink and Eric Shoubridge identified a mutation in *EFG1* (now known as *GFM1*), which encodes the mitochondrial translation elongation factor G1, in an infant with hepatocerebral syndrome (Coenen et al. 2004). The group of Nathan Fischel-Ghodsian reported a defect of mtDNA tRNA pseudouridylation due to mutations in the gene-encoding pseudouridylate synthase 1 (*PUS1*) in a recessive disorder known as mitochondrial myopathy and syderoblasric anemia (MLASA) (Bykhovskaya et al. 2004). As predicted in a lucid review by Howie Jacobs and Doug Turnbull (Jacobs and Turnbull 2005), this new class of disorders grew rapidly to include, besides translation elongation factors (Antonicka et al. 2006; Smeitink et al. 2006; Valente et al. 2007), the first defects in mitochondrial tRNA synthetase genes, *DARS2* and *RARS2*, the former reported by Marjo van der Knaap in patients with leukoencephalopathy and brain stem and spinal cord involvement (LBSL) (Scheper et al. 2007) and the latter by Orly Elpeleg in patients with pontocerebellar hypoplasia (Edvarson et al. 2007). In hindsight, however, the first report of a molecular defect involving mtDNA translation was the identification in 2003 of *LRPPRC* as the gene responsible for the French Canadian variant of COX-deficient Leigh syndrome (LSFC) (Mootha et al. 2003) (see above under "Indirect hits"). Considering the great number of components of the mtDNA translation apparatus, it is easy to see how the disorders described thus far must be just the tip the proverbial iceberg: stay tuned.

Defects of the inner mitochondrial membrane lipid milieu

Back in 1983, a Dutch pediatrician named Peter Barth (Fig. 12) described an X-linked recessive syndrome characterized by mitochondrial myopathy, cardiopathy, growth retardation, and leucopenia (Barth et al. 1983). Thirteen years later, Silvia Bione and Daniela Toniolo at the University of Pavia, Italy, identified the *G4.5* gene responsible for Barth syndrome and dubbed the proteins encoded by the gene "tafazzins," after Giacomo Tafazzi, a comic Italian television character who had the masochistic

Fig. 12 Peter Barth

habit of hitting himself on stage, which reminded Toniolo and her colleagues of their obstinate and almost masochistic pursuit of the elusive gene. The name has now been extended to the gene (*TAZ*) (Bione et al. 1996). In 2000, Peter Vreken in Ronald Wanders' group in Amsterdam established the relationship between *TAZ* mutations and cardiolipin, the most abundant phospholipid component of the IMM (Vreken et al. 2000). Two years later, Michael Schlame at New York University documented severe cardiolipin deficiency in tissues from Barth syndrome patients (Schlame et al. 2002) and 4 years after that showed that tafazzin is, in fact, a phospholipid transacetylase (Yu et al. 2006). Because cardiolipin does not act merely as a scaffold but has multiple functional roles, alterations of its concentration and composition may well have deleterious consequences on mitochondrial energy coupling or biogenesis, although the precise pathogenesis of Barth syndrome remains to be defined (McKenzie et al. 2006; Schlame and Ren 2006).

Defects of mitochondrial protein import

Considering that all but 13 mitochondrial proteins are synthesized in the cytoplasm and have to be imported into the organelle, and that the mitochondrial import is a complex process (Bolender et al. 2008), it is surprising that only a handful of disorders have been ascribed to defects of mitochondrial import. Although a few mutations in leader peptides causing specific enzyme defects were reported in the 1990s (Ledley et al. 1990; Takakubo et al. 1995), descriptions of genetic errors affecting the general import machinery first appeared in 2002, when the group of Carla Koehler at University of California - Los Angeles (UCLA) described mutations in the gene (*TIMM8A*) encoding the deafness/dystonia protein in patients with the X-linked Mohr-Tranebjaerg syndrome (not surprisingly characterized by deafness) (Roesch et al. 2002). In the same year, a Danish/French collaboration led to the discovery of mutations in the gene (*HSPD1*) encoding the import chaperonin HSP60 in patients with an autosomal dominant form of hereditary spastic paraplegia (HSP type 13; SPG13) (Hansen et al. 2002). Interestingly, in 2008, the Israeli group of Hanna Mandel found a homozygous missense mutation in the same gene (*HSPD1*) causing an early-onset autosomal recessive neurodegenerative disorder with brain hypomyelination and leukodystrophy (Magen et al. 2008). The only other known defect of mitochondrial import causes an autosomal recessive disease (dilated cardiomyopathy with ataxia, DCMA) clinically similar to Barth syndrome but due to mutations in *DNAJC19*, which encodes an IMM protein similar to a yeast co-chaperonin (Davey et al. 2006). Whereas it is likely that more disorders will be ascribed to defects of protein import, the meagerness of examples seems to validate the prediction made by Wayne Fenton 15 years ago that disruption of the general importation machinery would cause lethal conditions (Fenton 1995).

Defects of mitochondrial dynamics

Faithful to their bacterial origin, mitochondria move, fuse, and divide, often forming tubular networks that may favor a balanced and "convenient" distribution of energy within the cell (Bossy-Wetzel et al. 2003). In fact, mitochondrial dynamics is so extensive that—as David Chan aptly put it—"the identity of any individual mitochondrion is transient" (Chan 2007). Although this area of mitochondrial medicine opened only 10 years ago, it is no surprise that interfering with mitochondrial motility, fusion, or fission would result in disease, and especially neurological disease, both because the nervous system has high oxidative demands and because neurons have extremely long processes (think of an anterior horn cell motor neuron) requiring mitochondria to travel long distance (DiMauro and Schon 2008). In agreement with this concept, most disorders thus far associated with alterations of mitochondrial dynamics involve either the central or the peripheral nervous system. The first mutations were identified simultaneously in 2000 by Cécile Delettre and Christiane Alexander: they affected the *OPA1* gene, which encodes a guanosine triphosphate (GTP)ase involved in mitochondrial fusion, and resulted in autosomal dominant optic atrophy (DOA) (Alexander et al. 2000; Delettre et al. 2000). Four years later, peripheral nerves were recognized as targets of

mutations in a second gene (*MFN2*) also encoding a mitochondrial fusion protein, mitofusin 2, and resulting in Charcot-Marie-Tooth (CMT) type 2A neuropathy (Zuchner et al. 2004). In the same year, mutations in *KIF5A*, whose product, a kinesin, moves mitochondria along microtubules, were associated with a long-tract disorder, autosomal dominant hereditary spastic paraplegia (HSP) type 10 (SPG10) (Fichera et al. 2004). In the years that followed, other forms of CMT disease and both dominant and recessive variants of HSP have been associated with mutations in various mitochondrial motility proteins, and the role of altered mitochondrial dynamics in neurodegeneration and aging is being considered (Chan 2006) (DiMauro and Schon 2008).

One interesting story regards *OPA1* mutations, whose phenotypic spectrum has expanded enormously to include, besides optic atrophy, PEO, ataxia, deafness, and multiple mtDNA deletions, as documented by two collaborative European studies, one led by Patrick Chinnery (Hudson et al. 2008) and the other by Valerio Carelli (Amati-Bonneau et al. 2008). The fact that *OPA1* mutations cause multiple mtDNA deletions shows the difficulty of classifying mitochondrial diseases into clear-cut groups, as *OPA1*-related disorders belong both to the defects of mitochondrial dynamics and to the defects of intergenomic signaling. This dual identity is reflected at the functional level, as *OPA1* mutations impair both mitochondrial fusion and oxidative phosphorylation (Zanna et al. 2008).

New frontiers

I hope I have been able to convey the excitement that has accompanied—as it still does—the extraordinarily rapid development of mitochondrial medicine. This has been by necessity a cursory review, and I apologize to those colleagues who should have, but have not, been mentioned by name. Also, I have confined my narration to the "primary" mitochondrial diseases; that is, those associated, directly or indirectly, with defects of the respiratory chain. I alluded only in passing to the fact that mitochondrial dysfunction—especially defects of mtDNA maintenance and defects of mitochondrial dynamics—are involved in the pathogenesis of neurodegenerative diseases (DiMauro and Schon 2008). Ultimately, the goal of translational research is to come up with rational therapeutic strategies, a goal largely unfulfilled the for mitochondrial diseases, with few exceptions (primary CoQ_{10} deficiencies, MNGIE) to which I alluded in the text.

There are some interesting new areas of investigation that hold great promise for a better understanding of mitochondrial diseases, such as the realization that areas of physical contact between mitochondria and other cellular compartments have specialized functions and their disruption may play a crucial role in pathogenesis. Thus, Estela Area-Gómez in Eric Schon's laboratory has documented the preferential localization of presenilin-1 (PS1) and presenilin-2 (PS2) in a subcompartment of the endoplasmic reticulum closely associated with mitochondria (endoplasmic-reticulum-associated membranes, MAM) and has postulated that alterations of MAM function mediated by PS1 and PS2 mutations may explain many of the features of Alzheimer's disease (Area-Gomez et al. 2009).

Even more unorthodox is a report from the University of Genova, Italy, showing convincingly that oxidative ATP production takes place in bovine isolated myelin vesicles (Ravera et al. 2009). This is bolstered by ex vivo confocal laser scanning microscopy and immunohistochemistry showing that a respiratory-chain-like system is present in the myelin sheath of the optic nerve. Whereas the existence of extramitochondrial oxidative systems is not totally new (Mangiullo et al. 2008), the concept that myelin may be a "respiring wrap" providing ATP to the axon is exciting and may provide novel pathogenic mechanisms for neurological diseases.

In conclusion, mitochondrial medicine has had a brief and intense history, but the best (including effective therapy) is yet to come.

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