Mitochondria are the major site of energy production in the cell. It is not surprising, therefore, that an energy dependent tissue such as heart is affected by mitochondrial dysfunction. In this issue, Holmgren and colleagues report the cardiological findings and clinical course of 17 children with cardiomyopathy identified from a large cohort of children with mitochondrial disease. This is an important study that provides essential information concerning the cardiological features of what are becoming increasingly common disorders. Moreover, it is one of the first studies to provide some information about the natural history of cardiac disease in this group.

Mitochondrial disease in the context of this study means disease arising from defects of the mitochondrial respiratory chain (MRC). The MRC consists of five multi-subunit complexes embedded in the inner mitochondrial membrane. Its function is to conserve the energy released by the oxidative metabolism and use it to drive the phosphorylation of ADP to ATP. The MRC is unique for being under dual genetic control: proteins that make up four of the complexes are encoded either by chromosomal genes in the nucleus or on a DNA molecule contained inside the mitochondria themselves (mitochondrial DNA; mtDNA). Whilst mtDNA is physically separated from the nucleus, it remains entirely dependent on nuclear genes for homeostasis (maintenance, transcription, replication etc). It follows therefore that MRC disease can result from mutations affecting protein subunits in either genome, but also from defects affecting gene products involved with mtDNA homeostasis.

Mutations in mtDNA were first identified in 1988. Since then many more mutations have been identified causing a bewildering variety of clinical syndromes, often affecting more than one tissue, e.g. the heart, central nervous system (CNS) and skeletal muscle. More recently, mutations in nuclear genes encoding MRC proteins have been identified and these too give rise to disease affecting different tissues, including the heart.

Diagnosis of MRC disease currently depends on a combination of clinical suspicion supported by biochemical or histochemical demonstration of lowered MRC activity, usually in the affected tissue. Due to the difficulties of obtaining tissue, e.g. from the heart and CNS, and because skeletal muscle is often affected, albeit subclinically, this is the usual site for tissue diagnosis. Endomyocardial biopsy is beginning to replace this, but only in some centres. Mitochondrial or nuclear DNA analysis may also replace activity measurements, but this is only possible where the phenotype is one recognised to be associated with MRC dysfunction and often still follows the demonstration of lowered enzyme activity.

Notwithstanding recent advances, diagnosis of MRC dysfunction remains difficult. Biochemical assays are complicated, time-consuming and dependent on getting sufficient tissue. Histochemical analysis, which uses smaller amounts of tissue, can demonstrate cytochrome c oxidase (complex IV) and succinate dehydrogenase (complex II) deficiency, but is not yet able to demonstrate loss of activity in the other complexes. MtDNA analysis is also problematical. This genome is highly polymorphic and not all base changes, therefore, will be pathological. To complicate this further, individual mutations can cause very different phenotypes e.g. the same mutation can cause an encephalopathy or diabetes and deafness or progressive external ophthalmoplegia. That mtDNA mutations apparently arise secondarily to other disease
processes adds further difficulty. Deletions of mtDNA are found in a variety of pathological states, including late-onset idiopathic cardiomyopathy (see for example) and are, by some, even associated with the process of ageing itself.

Why should we be interested in mitochondrial disease, is it not just a rare curiosity? A recent population study looking at adults presenting to a neurological service specialising in mitochondrial disease, showed 6.7 per 100 000 had mtDNA mutations (minimum point prevalence figure). This figure does not include patients with disease secondary to nuclear mutation, except in two having multiple deletions. When these figures were combined with those at-risk (now including children of affected adults), the figure rose to 12.48 per 100 000. Clearly, not all of these will develop cardiac disease, the true incidence of which remains unknown. Taking into account that the figures are certainly underestimates, this study tells us, however, that mitochondrial disease in adults is far from rare. Furthermore, it is no longer the sole domain of neurologists; primary manifestations such as deafness, diabetes, gastrointestinal dysfunction and cardiomyopathy, amongst others, means that all physicians must be aware of these diseases.

A finding of potentially greater cardiological importance is that a polymorphism in the non-coding part of the mtDNA (a region called the D-loop) can be associated with increased risk of developing cardiomyopathy. Khogali and colleagues showed that a polymorphism at position 16 189 is associated with an increased risk of developing idiopathic dilated cardiomyopathy in two racially different populations. As yet we do not know how this mtDNA polymorphism exerts its effect. Speculation centres on the obvious role of mtDNA in the process of energy production, although no evidence confirming this currently exists.

Some of the accepted mutations causing cardiomyopathy are shown in Table 1. Only few produce cardiomyopathy alone or as the major clinical manifestation. Given the propensity of the same mtDNA mutations to produce very different phenotypes, however, this could be a sampling effect giving the impression of tissue specificity, albeit that true restriction of mtDNA defects is known. In the case of nuclear gene mutations, cardiomyopathy has been found in association with defects in SCO2, a protein involved in the assembly of complex IV, cytochrome c oxidase. The cardiac disease occurred early and together with lactic acidosis. Cardiomyopathy has also been seen in patients with other nuclear gene defects e.g. causing multiple mtDNA deletions. It is against this background that we must evaluate the work of Holmgren and colleagues. Few other studies have looked specifically at cardiomyopathy in mitochondrial disease. Of these, one is a case report and literature review (of similar case reports) and the others looked only at selected cases with defined mtDNA mutations. This current work includes children with both nuclear and mitochondrial defects and provides information about the clinical course of these patients. It is, therefore, the most complete study to date.

The criteria for the diagnosis of mitochondrial disease are sound and either based on biochemical and/or histochemical analysis or DNA analysis in the setting of a recognisable phenotype. In those cases where cardiac tissue was available, the reduced enzyme activity was confirmed in this tissue. Of 101 children with some form of mitochondrial disease, 17 (ca. 17%) had a cardiomyopathy. Interestingly, in five cases, the diagnosis of cardiomyopathy preceded the diagnosis of mitochondrial disease. Whilst not a population study, this is still good data and compares well with epidemiological data from the same group, suggesting 25% of children with mitochondrial disease will have cardiomyopathy. Since mitochondrial disease has an estimated minimum point prevalence ca. 5 per 100 000 children, with a similar figure in adults, 'mitochondrial' cardiomyopathy is a significant problem.

In this study, all cases in had the hypertrophic, non-obstructive type of cardiomyopathy. Earlier reports document both dilated and hypertrophic forms, but concentric hypertrophy appears to be that most commonly associated with MRC disease. Both in this study and earlier ones, cardiomyopathy can be the first feature of mitochondrial disease. In many instances, however, deafness, a resting metabolic acidosis, short stature or positive family history may be sufficient to alert one to the possibility of a mitochondrial aetiology.

What is very clear from this study is that cardiomyopathy in this group of patients carries a poor prognosis. Mortality among patients with no cardiac disease was 26% compared with 71% in those having cardiomyopathy. Those with an infantile debut and cytochrome oxidase deficiency did the worst of all, with a 100% mortality in the period of study and 75% dying of cardiac causes. Changes in clinical state can also occur quickly. These figures mean that those of us who care for patients with mitochondrial disorders must be alert to the possibility of subclinical cardiac disease. Moreover, once detected, these cases must be monitored carefully. The role of cardiac transplantation in this group has not been explored. The authors did identify five
candidates, one of whom received a new heart; three others died, two because of rapid deterioration, and interestingly, one improved. Whilst this study provides much needed insight into the natural history of cardiac disease amongst patients with mitochondrial disease, more information is needed.

This paper also raises several interesting questions. For example, is there a cardiological phenotype that we should recognise as ‘mitochondrial’? Hypertrophic, non-obstructive cardiomyopathy appears to be the most consistent finding, although dilated cardiomyopathy is also reported. More information is needed to judge whether dilatation is simply a later stage in the process and whether the finding of concentric hypertrophy is sufficient to act as the trigger. Another question concerns the choice of cardiological investigation in patients that have defined MRC disease? A chest X-ray and ECG are relatively minor and simple tests, but may not show early signs of hypertrophy. I would suggest that all patients with defined MRC disease should be referred for echocardiography. As the authors point out, however, if no cardiomyopathy is detected the first time, how often should we repeat it? As with all good studies, this work stimulates one to ask questions that are pertinent to the care of these patients.

### Table 1 Some of the mitochondrial and nuclear DNA defects associated with cardiomyopathy

<table>
<thead>
<tr>
<th>Genome affected</th>
<th>Gene</th>
<th>Site of defect</th>
<th>Cardiac manifestation</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitochondrial</td>
<td>tRNA leucine (UUR)</td>
<td>3260&lt;sup&gt;b&lt;/sup&gt;</td>
<td>DCM, LVH, WPW</td>
<td>Cardiomyopathy was the only feature in some affected. Myopathy in others. Biopsy showed COX neg/RRF.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3303&lt;sup&gt;b&lt;/sup&gt;</td>
<td>CHF</td>
<td>Patient presented in infancy with CHF and LA. SIDS in another. Earlier generations had myopathy with COX neg/RRF.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3243</td>
<td>HCM</td>
<td>This is the commonest mtDNA mutation. Is associated with very diverse phenotypes, the best known being MELAS.</td>
</tr>
<tr>
<td>tRNA isoleucine</td>
<td>4269</td>
<td>Infantile DCM</td>
<td>Isoleucine mutations appear to cause cardiomyopathy commonly, although in most cases this occurs in the setting of multisystem involvement. Most cause hypertrophy, but dilated cardiomyopathy is recorded.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4284</td>
<td>DCM</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4295</td>
<td>HCM</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4300</td>
<td>HCM</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>4317</td>
<td>HCM</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4320</td>
<td>HCM</td>
<td>The patient with 8348 mutation had HCM but went on to develop a DCM. One was dysmorphic. Multiple deletions of mtDNA are caused by nuclear gene defects. The precise defect is not given.</td>
<td></td>
</tr>
<tr>
<td>tRNA lysine</td>
<td>8348</td>
<td>HCM</td>
<td>The patient with 8348 mutation had HCM but went on to develop a DCM.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8363</td>
<td>DCM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nuclear</td>
<td>SCO2&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Different mutations</td>
<td>HCM</td>
<td>This is a cytochrome oxidase assembly protein, similar to SURF1&lt;sup&gt;d&lt;/sup&gt;. Two patients presented with acute cardiac decompensation plus LA.</td>
</tr>
<tr>
<td>Unknown&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>DCM</td>
<td></td>
</tr>
</tbody>
</table>

DCM=dilated cardiomyopathy; LVH=left ventricular hypertrophy; WPW=Wolf–Parkinson–White syndrome; COX neg=the presence of cytochrome oxidase negative fibres in the muscle (or cardiac) biopsy indicative of a disturbance of mitochondrial DNA; RRF=ragged-red fibres, these are fibres with accumulation of mitochondria under the sarcolemma and indicate the same as COX negative fibres; CHF=congestive heart failure; LA=lactic acidosis; SIDS=sudden infant death syndrome; HCM=hypertrophic cardiomyopathy; MELAS=myopathy, encephalopathy, lactic acidosis and stroke-like episodes.

Numbers relate to base position in the mitochondrial genome. The majority of mtDNA defects affect transfer RNA (tRNA), but others are known, including single deletions. This list provides examples of the type of defect that gives rise to cardiomyopathy and is not meant to be comprehensive. For a more detailed list and the original references for the individual mutations the reader is referred to the MITOMAP database.<sup>2</sup>

<sup>a</sup>These two mutations can present with only cardiomyopathy (3260, Reference<sup>12</sup>; 3303, Reference<sup>13</sup>)

<sup>b</sup>Numbers relate to base position in the mitochondrial genome. The majority of mtDNA defects affect transfer RNA (tRNA), but others are known, including single deletions. This list provides examples of the type of defect that gives rise to cardiomyopathy and is not meant to be comprehensive. For a more detailed list and the original references for the individual mutations the reader is referred to the MITOMAP database.<sup>2</sup>

<sup>c</sup>Reference<sup>6</sup>

<sup>d</sup>SURF 1 defects have not previously been found to give cardiomyopathy. The case in this paper is, therefore, unusual.

<sup>e</sup>Reference<sup>7</sup>
of patients with mitochondrial and cardiological disease.

Acknowledgement

I am grateful to Professor D.M. Turnbull for his helpful comments.

References