Familial Mediterranean Fever (FMF) was first described as a distinct disease entity, under the name of benign paroxysmal peritonitis in 1945. Although early on, it had several names, in the early sixties, the international medical community adopted the name suggested by the team led by Heller, which is, FMF. There are 3 classical aspects of the disorder that pertain to its name. First, Familial, as it is autosomal recessive, however, about half of the patients do not report a family history of the disorder. Second, Mediterranean, as it is prevalent in Mediterranean populations, namely, Jews (mainly non-Ashkenazi), Armenians, Turks and Arabs. Third, Fever, which is the most common component of the disorder. However, some patients do not realize that they are febrile during the attacks.

The clinical picture. The clinical picture consists of febrile and painful attacks that are usually of acute onset, variable frequency, and without a noticeable triggering factor but often occurring with menstruation, emotional stress or strenuous physical activity. The pain is usually severe occurring in the abdomen, chest and joints due to inflammation of the peritoneum, pleura and synovial membrane. The attacks last from 12-72 hours and abort abruptly but the arthralgia, if present, may last longer. The attacks start, most commonly, during childhood or adolescence, with about 80% of patients presenting their symptoms before the age of 20 years and very few after the age of 40 years. The clinical picture, intensity of symptoms and frequency varies from one attack to another and from one patient to another even within the same family. All patients suffer from abdominal pain at one point, and it is reported in 50% of patients as the first symptom. Chest pain is present in about 50% of attacks, usually in the form of unilateral pleurisy with diminished breath sounds, friction rub and may be effusion or collapse. Joint pain is present in about 50-75% of attacks and

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it is in the form of arthritis or arthralgia.\textsuperscript{5,12,15,16} The arthritis is usually monoarticular affecting the knee, hip or ankle joint.\textsuperscript{3,12,15,16} Some patients develop protracted arthritis, synovitis, muscle atrophy, erosions and juxta-articular osteoporosis.\textsuperscript{17-20} The most characteristic skin lesion is the erysipelas-like erythema, occurring in 3-45\% of attacks.\textsuperscript{21,22} It is a unilateral or bilateral, red, warm, swollen lesion about 10-15 cm in diameter, occurring below the knee or on the dorsum of the foot. The laboratory findings are non-specific and include leukocytosis with left shift, elevated erythrocyte sedimentation rate (ESR), high acute phase reactant titres like C-reactive protein (CRP), serum amyloid A (SAA), fibrinogen, haptoglobin, C3 and C4. There may be transient albuminuria and microscopic hematuria. In between attacks patients are free of symptoms. There may be slight discomfort, slight fever, splenomegaly, anemia, increased fibrinogen and increased immunoglobulins. Uncommon manifestations include acute scrotal inflammation;\textsuperscript{23-26} myalgia that can be mild, diffuse and of a short duration or protracted;\textsuperscript{27,28} headache, with meningeal irritation and increased cerebrospinal fluid (CSF) proteins and cells;\textsuperscript{29-31} impaired female fertility;\textsuperscript{32,33} pericarditis;\textsuperscript{34,35} vasculitis;\textsuperscript{36-38} purpuric lesions;\textsuperscript{22} and glomerulonephritis or nephropathy.\textsuperscript{37-40} One of the significant impacts of the disorder on the affected individual is the occurrence of amyloidosis as a complication. It is due to the deposition of AA protein, which is a cleavage product of SAA by the liver (acute phase reactant). Chemically, it is the same type of reactive amyloidosis, which takes place with chronic infections such as tuberculosis, bronchiectasis and rheumatoid arthritis.\textsuperscript{41} Amyloid A deposits in kidneys, adrenal glands, intestine, spleen, liver, lung, thyroid, heart, stomach and testes. Clinically, its deposition in the kidneys leads to persistent proteinuria, nephrotic syndrome and eventual renal failure.\textsuperscript{13} Intestinal malabsorption and adrenal insufficiency became recognized after the establishment of chronic renal dialysis as a treatment for renal failure and thus the prolongation of the lives of those affected. Routine urinalysis looking for early albuminuria should be followed by renal biopsy, rectal biopsy, bone marrow biopsy, abdominal fat aspiration or gingival biopsy.\textsuperscript{23,44} The biopsy should be stained with congo red and viewed under polarized light where AA gives an apple green colour. The treatment for amyloidosis is by hemodialysis and renal transplantation. Colchicine plays an important role in the prevention of amyloidosis and its reaccumulation in a grafted organ.\textsuperscript{45}

\textbf{Therapy.} Two initial publications introduced Colchicine as the primary therapy to reduce the frequency of FMF attacks.\textsuperscript{46,47} Its efficacy was established by few placebo-controlled trials.\textsuperscript{48-50} A daily regimen of 1-2 mg of oral Colchicine, introduced gradually, remains the recommended treatment since its introduction.\textsuperscript{51} It has been shown that this regimen is beneficial, also for the prevention of amyloidosis in all patients.\textsuperscript{10,52} in those already exhibiting proteinuria,\textsuperscript{23} and for the prevention of the reaccumulation of AA in a transplanted kidney.\textsuperscript{45} While being a miracle therapeutic option for FMF, Colchicine is not without its side effects.\textsuperscript{51} Many patients suffer from diarrhea and gastrointestinal upset but seem to tolerate it better when it is introduced gradually.\textsuperscript{51} In addition, Colchicine has been shown to induce lactose intolerance in FMF patients, which can be remedied by a lactose free diet and antiflatulents.\textsuperscript{54} Uncommon side effects include myopathy and peripheral neuropathy but mostly in older patients with impaired renal function.\textsuperscript{55} Although, it was reported that there was no teratogenic risk in 231 pregnancies in FMF patients on Colchicine, the same group later reported that the incidence of trisomy 21 was twice the expected.\textsuperscript{22} It is generally recommended to decrease the Colchicine dose during pregnancy, if possible, and to perform amniocentesis early in the 2nd trimester. The concentration of Colchicine in breast milk is very low, thus it seems safe for the child during lactation. While oral Colchicine has few risks, the intravenous administration of the drug carries major hazards and can lead to multiple organ failure and even death.\textsuperscript{56-59} Interferon \( \alpha \) is now considered as an adjuvant therapy for acute attacks in FMF patients who still suffer attacks while on Colchicine, or are resistant to the drug.\textsuperscript{60} Placebo controlled trials are still needed to evaluate its real value in the management of FMF attacks.

\textbf{The gene.} The successful mapping of the FMF gene was preceded by exclusion, using linkage analysis, of the AA gene, as well as, several other candidate genes that play a role in the inflammatory response.\textsuperscript{61-63} Linkage was tentatively suggested between the FMF gene and deoxyribonucleic acid (DNA) markers on chromosome 17, which proved to be a type 1 (\( \alpha \)) error.\textsuperscript{64} The gene, then named MEF, was finally mapped to the short arm of chromosome 16, with clear evidence for genetic homogeneity of the disorder.\textsuperscript{65-67} The genetic distance was determined at about 9 cM.\textsuperscript{68} The region containing the gene was then reduced to one million base pairs by linkage analysis, homozygosity studies and linkage disequilibrium.\textsuperscript{69-71} Polymorphic markers pulled out from a highly redundant contig spanning the one million base pairs further reduced the region to a 285 Kb fragment,\textsuperscript{72} while the other group managed to reduce the region to 250 Kb.\textsuperscript{72} Analysis of historical recombinant haplotypes further narrowed the candidate interval to a 200 Kb region.\textsuperscript{73} Utilizing different sophisticated molecular biology methodologies the region containing the gene was narrowed down to a 60-115 Kb.\textsuperscript{74,75} This lead to the final cloning of the gene for FMF, now called...
MEFV, by the 2 consortia independently and simultaneously. The gene is made of 10 exons, the complementary DNA (cDNA) is 3505 nucleotides long and it encodes for a 781 amino-acid long protein. With the cloning of the gene, 4 missense mutations, clustered in the 10th exon were identified, each of which is associated with a distinct haplotype. The identification of other mutations in the gene further established MEFV as the gene responsible for FMF.

The spectrum of mutations. Up until now, about 25 different mutations and polymorphisms are identified, most of them clustered in the 10th exon of MEFV. Due to the high prevalence of the disorder in the populations under study, it is sometimes difficult to distinguish a polymorphism from a disease causing mutation. Table 1 shows the 17 different mutations identified up to the end of the year 1999. The spectrum of mutations amongst the Arabs has not been adequately studied. The French consortium identified the M694I as a mutation corresponding to the ARA2 haplotype. The identification of other mutations in Arabs, A744S was present in one patient, E148Q was found on the same chromosome in Druze patients. One patient and the E148Q and the V726A were homozygous for the M694V mutation. It can now be deduced that phenotype - genotype correlations are not consistent across the different populations in whom the disease occurs with considerable frequency.

The protein. The protein has been named pyrin by the International consortium and marenostrin by the French consortium (after the Latin name for the Mediterranean sea; Mare Nostrum). The protein has domains with some homology to already existing human and other organism proteins. Based on the structure of the gene, the structure of the protein and its homology to other proteins, it is suggested that pyrin/marenostrin acts in the nucleus as a transcription factor and is probably a direct or indirect down regulator of inflammation. Animal models, whether naturally occurring or produced transgenically, may be another route towards the delineation of the protein function and its interactions with other proteins. In fact, the final goal would be to outline an inflammatory pathway in which the pyrin/marenostrin plays a role, and devise methods to counteract defaults in this pathway. This final goal can only be achieved by putting all the pieces of the puzzle together armed with clinical, molecular and epidemiologic tools for the dissection of this complex disorder.

**Table 1 - Common mutations identified in the MEFV gene.**

<table>
<thead>
<tr>
<th>Mutation</th>
<th>DNA site</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>E148Q</td>
<td>442 G-C</td>
<td>RE</td>
</tr>
<tr>
<td>E167D</td>
<td>501 G-C</td>
<td>ARMS</td>
</tr>
<tr>
<td>T267I</td>
<td>800 G-A</td>
<td>RE</td>
</tr>
<tr>
<td>P569S</td>
<td>1105 C-T</td>
<td>RE</td>
</tr>
<tr>
<td>R408Q</td>
<td>1223 G-A</td>
<td>RE</td>
</tr>
<tr>
<td>F479L</td>
<td>1437 C-G</td>
<td>ARMS</td>
</tr>
<tr>
<td>M680I</td>
<td>2040 G-C</td>
<td>ARMS</td>
</tr>
<tr>
<td>T681I</td>
<td>2042 C-T</td>
<td>RE</td>
</tr>
<tr>
<td>I692de1</td>
<td>2076-2078</td>
<td>RE</td>
</tr>
<tr>
<td>M694de1</td>
<td>2078-2080</td>
<td>RE</td>
</tr>
<tr>
<td>M694V</td>
<td>2080 A-G</td>
<td>ARMS</td>
</tr>
<tr>
<td>M694I</td>
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</tr>
<tr>
<td>K695R</td>
<td>2084 A-G</td>
<td>ARMS</td>
</tr>
<tr>
<td>V726A</td>
<td>2177 T-C</td>
<td>ARMS</td>
</tr>
<tr>
<td>A744S</td>
<td>2230 G-T</td>
<td>ARMS</td>
</tr>
<tr>
<td>R761H</td>
<td>2282 G-A</td>
<td>ARMS</td>
</tr>
</tbody>
</table>

**DNA** - Deoxyribonucleic acid;  
G - Guanine; C - Cytosine; A - Adenine; T - Thymine  
**RE** - Restriction Endonuclease Analysis  
**ARMS** - Amplification Refractory Mutation System
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References

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