inflammation (most often conjunctivitis and/or periorbital edema), and a distinctive migratory myalgia with overlying painful erythema may be present. TRAPS patients generally respond better to glucocorticoids than to prophylactic colchicine. Untreated, about 15% develop amyloidosis. The diagnosis of TRAPS is based on the demonstration of *TNFRSF1A* mutations in the presence of characteristic symptoms. Two particular variants, R92Q and P46L, are common in certain populations and may act more as functional polymorphisms than as disease-causing mutations. In contrast, pathogenic *TNFRSF1A* mutations, including a number of substitutions at highly conserved cysteine residues, are associated with intracellular TNFR1 misfolding, aggregation, and retention, with consequent ligand-independent kinase activation, mitochondrial reactive oxygen species production, and proinflammatory cytokine release. Etanercept, a TNF inhibitor, ameliorates TRAPS attacks, but the long-term experience with this agent has been less favorable. Perhaps because of the ligand-independent signaling abnormalities in TRAPS, IL-1 inhibition has been beneficial in a large percentage of the patients in whom it has been used. Monoclonal anti-TNF antibodies should be avoided, because they may exacerbate TRAPS attacks.

HYPERIMMUNOGLOBULINEMIA D WITH PERIODIC FEVER SYNDROME (HIDS)

HIDS is a recessively inherited recurrent fever syndrome found primarily in individuals of northern European ancestry. It is caused by mutations in mevalonate kinase (*MVK*), encoding an enzyme involved in the synthesis of cholesterol and nonsterol isoprenoids. Attacks usually begin in infancy and last 3–5 days. Clinically distinctive features include painful cervical adenopathy, a diffuse maculopapular rash sometimes affecting the palms and soles, and aphthous ulcers; pleurisy is rare, as is amyloidosis. Although originally defined by the persistent elevation of serum IgD, disease activity is not related to IgD levels, and some patients with FMF or TRAPS may have modestly increased serum IgD. Moreover, occasional patients with *MVK* mutations and recurrent fever have normal IgD levels. For these reasons, some have proposed renaming this disorder *mevalonate kinase deficiency (MKD)*. All patients with mutations have markedly elevated urinary mevalonate levels during their febrile attacks, although the inflammatory manifestations are likely to be due to a deficiency of isoprenoids rather than an excess of mevalonate. There is currently no established treatment for HIDS/MKD, although intermittent or continuous IL-1 inhibition and TNF inhibitors have been effective in small series.

THE CRYOPYRINOPATHIES, OR CRYOPYRIN-ASSOCIATED PERIODIC SYNDROMES (CAPS)

Three hereditary febrile syndromes, familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disease (NOMID), are all caused by mutations in *NLRP3* (formerly known as *CIAS1*), the gene encoding cryopyrin (or NLRP3), and represent a clinical spectrum of disease. FCAS patients develop chills, fever, headache, arthralgia, conjunctivitis, and an urticaria-like rash in response to generalized cold exposure. In MWS, an urticarial rash is noted, but it is not usually induced by cold; MWS patients also develop fevers, abdominal pain, limb pain, arthritis, conjunctivitis, and, over time, sensorineural hearing loss. NOMID is the most severe of the three disorders, with chronic aseptic meningitis, a characteristic arthropathy, and rash. Like the FMF protein, pyrin, cryopyrin has an N-terminal PYRIN domain. Cryopyrin regulates IL-1β production through the formation of a macromolecular complex termed the *inflammasome*. Peripheral blood leukocytes from patients with FCAS, MWS, and NOMID release increased amounts of IL-1β upon in vitro stimulation, relative to healthy controls. Macrophages from cryopyrin-deficient mice exhibit decreased IL-1β production in response to certain gram-positive bacteria, bacterial RNA, and monosodium urate crystals. Patients with all three cryopyrinopathies show a dramatic response to injections of IL-1 inhibitors. Approximately one-third of patients with clinical manifestations of NOMID do not have germline mutations in *NLRP3*, but have been found to be mosaic for somatic *NLRP3* mutations. Such patients also respond dramatically to IL-1 inhibition. Similarly, somatic mosaicism in *NLRP3* has been found in Schnitzler's syndrome, which presents in middle age with recurrent fever, urticarial rash, elevated acute phase reactants, monoclonal IgM gammopathy, and abnormal bone remodeling. IL-1 inhibition is the treatment of choice for Schnitzler's syndrome.

OTHER INHERITED AUTOINFLAMMATORY DISEASES

There are a number of other Mendelian autoinflammatory diseases in which recurrent fevers are not a prominent clinical sign but that involve abnormalities of innate immunity. The syndrome of pyogenic arthritis with pyoderma gangrenosum and acne (PAPA) is a dominantly inherited disorder that presents with episodes of sterile pyogenic monoarthritis often induced by trauma, severe pyoderma gangrenosum, and severe cystic acne, usually beginning in puberty. It is caused by mutations in *PSTPIP1*, which encodes a pyrin-binding protein, and the arthritic manifestations often respond to IL-1 inhibition. Patients with the recessively inherited deficiency of the IL-1 receptor antagonist (DIRA) present with a generalized pustular rash and multifocal sterile osteomyelitis, and show dramatic clinical responses to anakinra, the recombinant form of the protein they lack. IL-36 is another member of the IL-1 family of cytokines that is regulated by an endogenous receptor antagonist. The recessively inherited deficiency of the IL-36 receptor antagonist (DITRA) presents with episodes of generalized pustular psoriasis and dramatic systemic inflammation.

Whereas PAPA, DIRA, and DITRA all involve mutations in IL-1-related molecules, other autoinflammatory diseases are caused by mutations in other components of innate immunity. *Blau's syndrome* is caused by mutations in *CARD15* (also known as *NOD2*), which regulates nuclear factor-κB activation. Blau's syndrome is characterized by granulomatous dermatitis, uveitis, and arthritis; distinct *CARD15* variants predispose to Crohn's disease. Recessive mutations in one or more components of the proteasome lead to excessive interferon signaling and the syndrome of chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE), a severe form of generalized panniculitis. De novo gain-of-function mutations in TMEM173, encoding the stimulator of interferon genes (STING), cause severe vasculopathy and pulmonary fibrosis. Recessive loss-of-function mutations in CERCR1, encoding adenosine deaminase 2 (ADA2), cause a vasculopathy that can manifest as livedoid rash, early-onset lacunar strokes, or polyarteritis nodosa.

Finally, it should be noted that a number of common, genetically complex disorders are now sometimes considered autoinflammatory, because of evidence that components of the innate immune system, such as the inflammasome, may play a role in the pathogenesis. Two prominent examples are gout and atherosclerosis. Large clinical trials of IL-1 inhibitors have been initiated in both conditions.