phagocytic vacuole. Thus, the role of ROS in the killing process is not as direct as previously thought, although, ROS are necessary to increase phagosomal osmolarity. Mice made deficient in neutrophil-granule proteases, but normal in respect of superoxide production and iodinating capacity, were unable to resist staphylococcal and candidal infections, suggesting that proteases are primarily responsible for the destruction of the bacteria [48]. Further research then showed that microbial killing and digestion were abolished when the BK_{Ca} channel was blocked, revealing an essential and unexpected function for this K^+ channel in the microbicidal process [48].

Defective inflammatory responses

In addition to recurrent life-threatening infections, patients often develop sterile granulomas in hollow organs, liver, lymphoid tissue and skin, without clinical evidence of infections [49]. The mechanisms involved in this aberrant inflammatory response are unknown. Inflammatory responses are finely balanced between pro-inflammatory and anti-inflammatory mediators and are important in generating an effective primary immune response and in clearing infection. Cultured cells from CGD patients have been shown to be deficient in their ability to produce anti-inflammatory mediators [50] and that neutrophils from these patients are defective in their ability to expose phosphatidylserine (PS), which is a recognition factor for phagocytic cells to clear apoptotic cell bodies. The externalized PS molecules on apoptotic cells, and subsequent internalization and degradation of apoptotic cells, is crucial to prevent the activation of an inflammatory response and persistence of inflammatory cells that do not undergo apoptosis and are not phagocytosed leads to an increase of necrosis and release of toxic granule contents that can cause chronic inflammation. Recently, we have shown that the rate of phagocytosis of apoptotic CGD neutrophils is also reduced (unpublished observations). It is not known why this occurs and further studies of the mechanisms of neutrophil apoptosis are necessary to understand the pathophysiology of its deficiency in CGD. Failure to successfully resolve inflammation can underlie the persistent inflammatory responses in CGD patients, as manifested by colitis, urinary tract obstruction, dysphagia, gastric outlet obstruction and chorioretinitis.

Interferon-gamma therapy for CGD

In the late 1980s the potential of interferon gamma was investigated as a prophylactic therapeutic agent for CGD as preliminary studies in CGD patients demonstrated that brief in vitro or in vivo administration of recombinant IFN-γ (rIFN-γ) significantly enhanced phagocyte $O2^{-\cdot}$ production and *Staphylococcus aureus* bacterial killing. In two patients with variant X-linked CGD, rIFN-γ treatment in vivo was also associated with increased spectral levels of neutrophil cytochrome-b_{558} [51]. Subsequent studies found little evidence for transient increases in $O2^{-\cdot}$ production following rIFN-γ therapy, where $O2^{-\cdot}$ production was not sustained or associated with any change in cytochrome-b_{558} levels [52]. In some patients, rIFN-γ therapy was associated with the appearance of a small subset of circulating monocytes (1% to 20%) that were NBT-positive, suggesting that one possible mechanism by which rIFN-γ may benefit CGD patients was by partially correcting the respiratory burst defect in a subset of monocytes. Although it seemed that rIFN-γ therapy in the vast majority of CGD patients was not due to enhanced neutrophil NADPH oxidase activity, the mechanism of rIFN-γ action in CGD patients remains unknown. A study by Ahlin *et al.* [53] showed that rIFN-γ treatment of patients with CGD was associated with augmented production of nitric oxide by polymorphonuclear neutrophils. A comprehensive follow up study of 76 patients with CGD who received rIFN-γ found that its prolonged use in patients with CGD appeared to be safe and showed persistent reduction in the frequency of serious infection and mortality [54]. Recent studies looking at the cytochrome-b_{558} gene expression in Brazil [55] and Japan [56] found increased total messenger RNA (mRNA) levels in the CGD patients' cells suggesting that rIFN-γ improved mRNA splicing and concluded that rIFN-γ partially corrects a nuclear processing defect. These studies have lead to the consensus that only rare variants with splice site mutations can be improved with rIFN-γ therapy. rIFN-γ therapy is relatively expensive due to the high cost of recombinant human interferons, the large doses and lengthy course of administration necessary to achieve maximum response rates in recipients, and is not routinely administered prophylactically in Europe.

A cure for CGD

Following the successful use of allogeneic bone marrow transplants to treat children with severe combined immune deficiency [57]. Goudemand and colleagues [58] made the first attempt to treat a case of CGD using bone marrow transplantation (BMT). Although in this case the transplant failed after two months due to tissue rejection recent advances in BMT expertise and technology have led to BMT becoming a successful treatment option for CGD patients. A recent review of cases revealed that 20 of 24 CGD patients are alive and disease free 1–7 years after transplant [59]. BMT can be successfully performed for CGD and remains an attractive option for children who have an HLA matched sibling donor and useful in selected very severe cases in which prophylactic therapy is problematic, although in many cases donors can be hard to find.

Gene therapy involves the permanent genetic correction of hematopoietic stem cells in which a vector is used to