Outlook

The beginning and the end of Bruno Speck's scientific career were milestones in the history of severe aplastic anaemia (SAA). In the early 70s, when Bruno Speck became involved with SAA, the disease had just begun to emerge as a distinct entity with an invariably fatal outcome in its severe form. Though diagnosis was possible, the available therapeutic tools failed to alter the course of the disease; spontaneous remissions were extremely rare. Bone marrow transplantation (BMT) brought new hope. Bruno Speck set out to change the poor outlook for patients with SAA and to explore the use of antilymphocyte globulin (ALG) for patients not eligible for BMT. Together with the haematology community, he achieved a major therapeutic breakthrough. Today, SAA has lost its stigma as a fatal disease, the prognosis for individual patients is excellent. However, many problems remain and we are again at a crossroads with the disease.

The near future may change our concepts of SAA, both in terms of the understanding of its pathophysiology and the development of new or more specific therapeutic tools. The solution to 'Damaschek's riddle', i.e. the cause for the close connection between SAA, paroxysmal nocturnal haemoglobinuria and myelodysplastic syndrome may become unravelled. New haematopoietic growth factors or new combinations of cytokines may turn out to be more effective than those currently in use. Prevention of apoptotic death of stem cells as a logical approach may prove beneficial. Stem cell transplantation as a curative treatment of SAA is developing rapidly. Traditional BMT has been supplemented by extension of the pool of potential donors and the detection of new possible sources of stem cells. Through rapidly expanding registries of unre-

lated donors and cord blood banks together with refined HLA typing and recognition of 'permissible' mismatches, it may soon become possible to find an appropriate stem cell graft for the majority of SAA patients. In addition, toxicity of the procedure is likely to be reduced by the use of low-intensity conditioning regimens in the near future, which may provide a 'graft-versus-aplasia' effect with less unwanted side-effects. The recent detection of cells in the brain capable of haematopoietic reconstitution opens a new experimental world: theoretically, the deficient haematopoietic stem cell pool in SAA might be restored by autochthonous stem cells, which are unlikely to be affected by the disease. Such an approach appears futuristic at the present time and may never be realized in the form that we now anticipate. However, looking at the fascinating history of ALG in retrospect, I conclude that the potential of 'new' possibilities is essentially unpredictable. Originally, ALG was thought to be beneficial in SAA by preventing rejection and graft-versus-host disease after transplantation of mismatched bone marrow. Only later did it become clear that ALG itself was the active principle as an immunosuppressant. Thus, the concept was wrong but the application right. The serendipity of investigators, collaboration of different teams involved in the investigation of the concept, the effort to collect international data, and creativity of the mind towards their correct interpretation contributed independently to the ultimate success of ALG. It is likely that future improvements in the treatment of SAA will depend on a similar 'mix of ingredients'.

Alois Gratwohl, Basel