

Haematology and Blood Transfusion

Hämatologie und Bluttransfusion

# Aplastic Anemia

**Pathophysiology and Approaches to Therapy**

Edited by

H. Heimpel, E. C. Gordon-Smith,

W. Heit and B. Kubanek



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H. Heimpel, E. C. Gordon-Smith,  
W. Heit and B. Kubanek

With 81 Figures and 71 Tables



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## Foreword

Research on aplastic anaemia has until recently been limited to clinical description, morphology and epidemiology. New methods to culture haemopoietic cells, and advances in our knowledge of proliferation and differentiation in the haemopoietic cell system opened a new area of scientific interest for this "prototype" of haemopoietic failure. In addition, bone marrow transplantation became not only a clinical method of treatment, but also a source of data useful for the discussion of pathophysiological models of aplastic anaemia.

This situation prompted us to arrange an international conference on aplastic anaemia, with particular emphasis on its pathophysiology and the rationals of the current therapeutic approaches. This conference was held at Schloss Reisensburg from July 20–22, 1978 with the participation of both experimental and clinical scientists active in this field or in related areas of research. The proceedings of the symposion reflect the present knowledge as well as the many new questions which arose from the discussions.

The editors are gratefully indebted to the participants of this meeting, to Gerlinde Trögele and all the co-workers of the University of Ulm engaged in preparation of this symposium and of this volume, and last not least to all sponsors who provided the financial basis for this scientific event.

Ulm, September 1979

H. Heimpel  
E. C. Gordon-Smith  
W. Heit  
B. Kubanek

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# **1 Introduction**



## Introduction

H. Heimpel

We are happy to welcome all of you on behalf of the Organizing Committee and the University of Ulm at this symposium on aplastic anemia. When we asked some of you one year ago whether there would be interest in such a meeting, we met a positive response and felt that the progress of the last five years made it useful to discuss the problems of this disease between clinicians and experimental investigators. The fact that, at a time overloaded with meetings and congresses, so many prominent and busy scientists followed our invitation demonstrates the current interest in this model of hemopoietic failure. I hope that, together with the special atmosphere of Schloss Reisingburg, this common interest will produce many stimulating and fruitful discussions. We appreciate that you made the effort to come here from many countries, and at this time we would like to thank the public and private sponsors who enabled us to arrange this meeting.

To introduce the subject, I want to give you a short summary on the evolution of research on aplastic anemia. Aplastic anemia was first described in 1888 by one of the real pioneers of biomedicine, Paul Ehrlich in Berlin, who outlined in his paper the clinical essentials and basic pathophysiology of the disease still valid today. 10 years later, Santesson from USA, in a paper written in German, detected that the aplasia may be due to an external factor, benzene. After the detection of Vitamin B12 and iron as therapeutics in anemia, it was shown in the thirties that these drugs were not effective in aplastic anemia, suggesting a basic difference from other types of hemopoietic failure.

An important stimulus for further research was the observation, that the antibiotic chloramphenicol could induce aplastic anemias, but did so only in a minority of exposed individuals. This pointed to the importance of intrinsic, possibly genetic predisposition. Despite the efforts of many investigators to elucidate a possible genetic background, the question of individual hypersensitivity has remained open to the present day.

When autoallergy was detected as a mechanism of disease, autoantibodies to blood cells were described in different forms of pancytopenia and thought to be responsible for the hemopoietic aplasia; however, this theory did not stand later criticism, and today we are inclined to believe that the reactions observed were due to HLA-allo-antibodies not known at this time.

A third external factor, the hepatitis virus, was described in 1955 and this relationship was later supported by many observations. A large review of such cases was made by Dr. Camitta who is going to speak about the viral induction of aplasia at this meeting. As in the case of chloramphenicol or phenylbutazon, we have been able to identify the external noxious agent, but we still do not know the link between virus infection and stem cell injury, and we do not know why only

very few people with virus infection develop aplasia. Is the primary target actually the hemopoietic stem cell? Or is the primary target stromal tissue? Does viral infection trigger immunological reactions? The problem of "soil or seed", that means the primary role of hemopoietic stem cells or their supporting microenvironment had been raised earlier, for example by Krospe and Crosby 1971. This question has not yet been answered and there may be aplastic anemias of both types.

For a long time, no successful treatment was available for aplastic anemia except blood transfusions and supportive care. In 1959, androgens were found by Shahidi and Diamond to be useful in childhood aplastic anemia, mainly of the congenital types. After many years of experience with androgens, their therapeutic value and their mechanism of action are still a matter of discussion. Further therapeutic alternatives were opened by the work of Dr. D. Thomas on allogeneic bone marrow transplantation, inducing a new area of research activities on aplastic syndromes.

In recent years, many new data were obtained by the application of clonal stem cell assays after Pike and Robinson in 1971 adapted the techniques to human material. The last and most fashionable data come from the immunologists and suggests suppressor T-cells to be of pathogenetic importance. These data were recently published from a group in the Sloan Kettering Institute and soon followed by similar ones from other centers. I personally believe that it has not been unequivocally shown that suppression of hemopoietic stem cells exists in aplastic anemia and the relevance of these findings should be discussed very intensively at this meeting.

In spite of the progress made by all these observations, one has to admit that the pathogenesis of aplastic anemia is not very well understood. The goal of our symposium is to discuss recent advances and to establish working hypotheses from results obtained in the different fields of research. We should particularly try to find out to what extent the many and sometimes confusing experimental data are in agreement or disagreement with clinical observations.

The lectures of the first session are thought to summarize the most important clinical data. One of the main problems to be discussed may be whether aplastic anemia is one disease, or rather the non-specific end results of different underlying pathological mechanisms. This is an important question for the clinician as well as for the experimental researcher who works with material from such patients.

The following session on stem cells leads to the central topics of aplastic anemia research. We hope that in addition to the conventional clonal assays, culture techniques evaluating proliferation capacity of stem cells will be included, and that application of such techniques to human clinical research will be stimulated. One important aspect is the use of animal models. We invited Dr. A. Morley to contribute at this point, and we are sorry that he is not able to participate. In the general discussion on stem cells we hope to identify what we have really learned and what we are going to learn from experimental models and stem cell techniques for the human situation.

The session on therapeutic approaches continues the analysis of the natural course of the disease. For this symposium, we would like to use therapy as a clinical

experiment done on human aplastic anemia. The main emphasis will therefore be placed on how and why certain treatments are effective or ineffective, rather than on clinical details. At the end of this symposium we hope to come to a better understanding of the results of various treatment modalities. This is particularly true for bone marrow transplantation, which in spite of its actual merits may still be regarded as experimental therapy.

The question of immun-mechanisms seems to be at present the most controversial matter in the pathogenesis of aplastic anemia. We particularly appreciate the presence of Dr. Thorsby from Oslo, who agreed to introduce this session, even though he only received our invitation shortly before the symposium. We expect the chairmen to use their experience in various *in vitro* and *in vivo* systems to look rather critically on the many data, which have arisen from experiments with serum and lymphatic cells from aplastic anemia patients. The end point of such experiments is usually a clonal stem cell assay, and in this respect the results of the previous stem cell session may be useful when the validity of the immunological data is discussed.

In the final general discussion, at the end of the second day, we would like to bring together the data and conclusions of the previous sessions, in an attempt to recognize which questions were to be answered and which problems may be subjected to further investigation in the near future. I am afraid that after two days we will not have solved the riddles of aplastic anemia, however, I hope that after this symposium clinicians, stem cell researchers, transplanters and experimental immunologists will have better mutual understanding of their work, and that we will know better what kind of future research projects may help to understand the disease aplastic anemia in the forthcoming years. I believe that better knowledge of the pathophysiological mechanisms is the only way for relevant progress in the prevention and therapy of this disease.



