studied a large number of patients. Koethe et al.
whose work on factor D was apparently cited by Dr Larcher et al. made no measurements of factor D in sickle cell disease.

The complement system deficiency and its relationship to high infection rates in sickle cell disease deserve further attention. Our studies currently indicate that the ratio of haemolytic to immunochemical factor B level may be a convenient and relatively simple index of the complement abnormality in sickle cell disease. We have shown that the abnormality is not produced by reduced synthesis of complement proteins, as speculated by Dr Larcher et al. but rather by excessive complement activation which depletes functionally active factor B and possible other factors from serum. These factors may therefore not be as available for defence against infection. We have also shown that hypercatabolism of C3 is linked to the intravascular component of the haemolytic process in sickle cell disease.

The therapeutic implications of these and other studies of immunity related phenomena in sickle cell disease are not clear. Because of their rapid catabolism (normally 2% of the plasma pool per hour in the case of factor B) it may not be rational to attempt to correct the abnormality by replacing deficient proteins as fresh plasma. However, if factor B hypercatabolism is in fact produced by the haemolytic process in sickle cell disease, it may be possible to reverse this abnormality (temporarily) by exchange transfusion with normal compatible erythrocytes. Such transfusions have been shown to reverse the functional abnormality of the spleen in early childhood in sickle cell disease, and may therefore benefit those patients with fulminant or resistant infections.

References


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Dr Larcher and co-workers comment:

We thank Dr Wilson for his interest in our work on complement deficiency states in children with sickle cell disease and apologise for our oversight in not citing the further work which he and his co-workers have published in elucidating the nature of these defects.1–3 However, in this preliminary study, whose major purpose was the identification of complement deficient states in a UK population of children with sickle cell disease, it seemed inappropriate to speculate comprehensively on the precise mechanism of these defects, especially since we did not have the data which Dr Wilson cited4–8 on the children we studied. Although we speculated that defective synthesis of complement components might contribute to the observed deficiency states we feel that we did not give this possibility more weight than the alternative explanation of excessive complement activation which Dr Wilson and his co-workers demonstrated in about half of their adult patients.1–8

The patients in our series were younger than those in whom metabolic studies were performed (none of the latter being less than 18 years of age.) Ethical problems in performing isotope studies in children are considerable and such studies might be difficult to justify along the guidelines laid down by the British Paediatric Association for research in children,4 until more is known about the relationship between complement deficiency and infection in these subjects. The establishment of normal ranges in such turnover studies in age matched controls would also be difficult to justify but crucial in the interpretation of data obtained from children with sickle cell disease. Measurement of C3d levels in plasma would be a more acceptable means of detecting complement activation in children, but levels of C3d were normal in the limited number of plasma samples we examined.

Our finding of at least two distinct complement defects suggests that further studies of the alternative pathway of complement in children with sickle cell disease are indicated. The possible role of factor D would seem to require further study since, although Koethe et al. did not measure factor D they concluded that 'sera from patients with sickle cell disease have reduced C3 proactivator convertase activity’ (factor D activity). The nature of the complement defect in yeast opsonisation deficiency awaits elucidation although deposition of C3b on yeasts is slow in sera from such patients. Such defects appear to be in part genetically determined so that protective synthesis of regulator proteins in children with this deficiency cannot yet be excluded.

We agree with Dr Wilson that complement appears to be important in maintaining host defences against infection, especially as the occurrence of severe defects in patients with severe liver disease appears to be related to their high incidence of infection. Plasma infusion does have some apparent therapeutic benefit in these patients though it clearly cannot be advocated as a prophylaxis. In this context, the recent report of the beneficial effects of plasma infusion on patients in sickle cell crisis is of interest,8 although such infusions were given for non-immunological reasons.
Patients with sickle cell disease are more prone to infection than others, and any means of identifying those at greatest risk, such as those described by Dr Wilson, should prove of benefit.

References


Medical ethics working group

Sir,

The Society for the Study of Medical Ethics has established a multi-disciplinary working group, with generous funding from the Leverhulme Trust, to study the ethics of clinical research investigations on children. The group has been meeting for 12 months, and hopes to publish its report at the end of this year.

Already a number of paediatricians have sent me interesting and useful examples of paediatric research that has rightly or wrongly caused ethical problems, and I am extremely grateful to them. The working group is still interested to hear of any paediatric research projects or innovative therapies which have caused ethical problems, whether to the researchers, to research ethics committees, or to others. Details will be treated in confidence and should be sent to me.

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Book reviews

The Immunology of Infant Feeding.

Though a book of great interest, it should be recognised that The Immunology of Infant Feeding is more for those with special concern with childhood nutrition, infant feeding, or developmental immunology and allergy, than health care workers with a general paediatric interest.

The book presents papers given at an international conference in 1980, and it is useful in stating several position papers related to this important and interesting subject. The field had advanced considerably during the 1970s, but was due for a review at this stage. It may be a disadvantage that both the experience and new observations reported came mainly from workers in the USA, the United Kingdom, and northern Europe rather than the wider world, where gastrointestinal immunity is more constantly challenged. Those contributing are acknowledged experts in their fields, and their contributions are logically arranged by the editor, who has achieved a satisfactory evenness of style.

The chapters are essentially derived from papers from the 13th course of the International School of Medical Sciences, which was held at Erice in 1980. They number 13, and each is followed by individual and modern bibliography, but no reported discussion. The initial papers are concerned with the functions of the IgA system and other protective mechanisms. The development of the themes concerned with IgA is particularly interesting and embraces the traffic of lymphoid cells and the possibility that antigen/IgA complexes may be 'tolerogenic'. This leads to the complementary chapter dealing with normal and abnormal food antigen handling in atopy, with interesting experimental results.

The sections dealing with the bacteriostatic effect of human milk present perhaps too narrow a view in the light of the fact that the position of lactoferrin has been to some extent stabilised. The very interesting early studies with this protein have not so far provided opportunities for clinical developments with therapeutic applications. The following chapter, concerned with the bacterial flora of the gut, and that concerned with virus infection, outline some of the ecological features of the intestinal bacterial population.

The middle part of this informative book is devoted to some of the clinical patterns of the failure of immunity, especially in the context of malnutrition, and in relation to low antibodies. The insights here represent the strong influence of Professor Soothill, who contributes one of the papers and the preface, and who has long been associated with allergy and immunodeficiency. These are important and fruitful contributions, however, which are of great theoretical interest.

The final chapters are unfortunately not so satisfactory in the context of the main theme of the work. Brian Wharton's excellent papers concerned with the nature and potential of modern artificial feeding preparation do not easily point the way through the problem of replacing the protective and immunologically useful factors to be found in breast milk. There remains no way of replacing this with a substitute based on the milk of another species, a position emphasised by Hanson's final chapter which refers to implications for immunisation and introduces the remarkable concept of the enterotheretic axis.

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