in each sample remained Poisson in form (as predicted by stochastic models of immigration-death processes[18]). Within a cohort of inbred mice repeatedly exposed to the same level of infection, underdispersion in parasite numbers per host would have resulted, especially in the latter part of the experiment when mean worm burdens declined, if the host mortality were linked directly to worm burden[19] (the rapid elimination of heavily infected animals acting to decrease the variance within a sample).

More generally, we agree that mice are not ideal models for the study of schistosome infections of man. However, our aim was to show that experimental studies of immunity to helminth parasites, based on repeated exposure to low levels of infection (as is thought to occur in human communities within areas of endemic infection), produce results that are not always in accord with more conventional experimental designs based on primary infection and a single subsequent challenge.

R. M. ANDERSON
J. A. CROMBIE

Department of Pure and Applied Biology, Imperial College, University of London, London SW7 2BB, UK

R. M. MAY

Department of Biology, University of Princeton, Princeton, New Jersey 08540, *USA*

1. Anderson, R. M. & May, R. M. *Nature* **315**, 493-496 (1985).
2. Anderson, R. M. & May, R. M. *Adv. Parasit.* **25**, 1-101 (1985).
3. Mahmoud, A. A. F., Arap Siongok, T. A., Ouma, J., Houser, H. B. & Warren, K. S. *Lancet* **i**, 849-851 (1983).
4. Wilkins, H. A., Goll, P. H., Marshall, T. F. de C. & Moore, P. J. *Trans. R. Soc. trop. Med. Hyg.* **78**, 216-221 (1984).
5. Butterworth, A. E. *et al. Trans. R. Soc. trop. Med. Hyg.* **78**, 108-123 (1984).
6. Butterworth, A. E. *et al. Trans. R. Soc. trop. Med. Hyg.* **79**, 393-408 (1985).
7. Bensted-Smith, R. *et al. Trans. R. Soc. trop. Med. Hyg.* (in the press).
8. Elkins, D., Haswell-Elkins, M. & Anderson, R. M. *Trans. R. Soc. trop. Med. Hyg.* (in the press).
9. Hliang, T. in *Ascariasis and its Public Health Significance* (eds Crompton, D. W. T., Nesheim, M. C. & Pawlowski, Z.) 21-48 (Taylor & Francis, London, 1985).
10. Schad, G. A. & Anderson, R. M. *Science* **228**, 1527-1540 (1985).
11. Bundy, D. A. P. *Trans. R. Soc. trop. Med. Hyg.* (in the press).
12. Arap Siongok, T. K. *et al. Am. J. trop. Med. Hyg.* **25**, 274-284 (1976).
13. Abdel-Wahab, M. F. *et al. Am. J. trop. Med. Hyg.* **28**, 868-874 (1980).
14. Ongom, V. L. & Bradley, D. J. *Trans. R. Soc. trop. Med. Hyg.* **66**, 835-851 (1972).
15. Hailt, R. A., Cline, B. L., Ruiz-Tiben, E., Knight, W. B. & Berrois-Duran, L. A. *Am. J. trop. Med. Hyg.* **29**, 1228-1240 (1980).
16. Barnish, G., Jordon, P. Bartholomew, R. K. & Grist, E. *Trans. R. Soc. trop. Med. Hyg.* **76**, 602-609 (1982).
17. Crombie, J. A. & Anderson, R. M. *Nature* **315**, 419-483 (1985).
18. Anderson, R. M. & Medley, G. *Parasitology* **90**, 629-660 (1985).
19. Anderson, R. M. & Gordon, R. *Parasitology* **85**, 373-398 (1982).

Cause of the 'inhibitor' phenotype in the haemophilias

Following the paper by Gitschier *et al.*[1], we feel that a brief comment on their data and our earlier findings in haemophilia B[2] may help to clarify, or generate ideas that may lead to a better understanding of, the causes of the 'inhibitor' phenotype, a necessary step in the development of a completely successful treatment.

In 1983 we reported gross gene deletions in four out of five haemophilia B patients with the inhibitor phenotype, in support of the hypothesis that haemophilia B patients with inhibitors are predisposed to develop antibodies to factor IX as a result of mutations that prohibit the synthesis of a sufficiently normal factor IX protein and thus prevent the development of immune tolerance to normal factor IX. Of course, whether such a predisposition results in the inhibitor complication may depend on other factors such as the patient's genetic background and environmental experience: for example, the intensity and duration of treatment with normal coagulants. In four of our patients the predisposing mutation was a deletion of two-thirds or more of the factor IX coding sequence, but, of course, point mutations, frameshift mutations or shorter deletions could have had the same effect if they had occurred at positions which prevented the synthesis of a protein capable of inducing immune tolerance to normal factor IX. For example, the predisposing mutations might interfere with synthesis or processing of RNA, or might be mutations that affect the translation of messenger RNA into protein.

Previously, we predicted that gross changes of the factor VIII(c) gene might be found in haemophilia A patients with inhibitors. Now, Gitschier *et al.*[1] report a patient with a deletion involving exon 26 which codes for the last 51 amino acids of factor VIII, and another with an aberrant translation stop codon arresting translation of the factor VIII mRNA 26 amino acids prematurely, neither of which are associated with antibodies to factor VIII. Conversely, a patient with a different aberrant stop codon generating a truncated protein that is 124 amino acids short and another patient with a deletion comprising exons 23-25 which code for 157 amino acids, have both developed inhibitors. Such results seem in keeping with our observations in haemophilia B, since the loss of normal factor VIII epitopes in the latter two cases would be expected to be greater than in the first two cases of Gitschier *et al.*[1], and hence more likely to result in defective immune tolerance to normal factor VIII.

In haemophilia B four further inhibitor patients have shown gross gene deletions: one in the United Kingdom[3] and three in Italy (H. J. Hassan *et al.*, F. Bernardi *et al.* and M. Pecorara *et al.*, personal communications). These findings, of course, are at variance with the results of Gitschier *et al.* in haemophilia A, as many of their inhibitor patients did not show easily detectable gene defects. However, this is not the crux of the matter. What matters is whether the inhibitor complication arises in patients with mutations preventing the development of immune tolerance or not. In other words, is the discrepancy between the findings in haemophilia A and B principally a result of a more complex aetiology of the inhibitor complication in haemophilia A or caused by the plurality of factor VIII defects which can prevent the development of immune tolerance to normal factor VIII, in keeping with the example of haemophilia B?

We believe that the characterization of both the gene defects and the epitope specificity of the antibodies against factor VIII found in inhibitor patients would clarify the situation and reveal important immunological features of this coagulation factor.

F. GIANNELLI
Paediatric Research Unit, United Medical Schools of Guy's and St Thomas's Hospitals, Guy's Tower, London Bridge, London SE1 9RT, UK

G. G. BROWNLEE
Sir William Dunn School of Pathology, South Parks Road, Oxford OX1 5RE, UK

1. Gitschier, J. *et al. Nature* **315**, 427-430 (1985).
2. Giannelli, F. *et al. Nature* **303**, 181-182 (1983).
3. Peake, I. R., Furlong, B. L. & Bloom, A. L. *Lancet* **i**, 242-243 (1984).