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Reply

M. Hontebeyrie-Joskowicz is absolutely right to draw attention to the denervation-related digestive pathology observed in the chronic phase of Chagas disease: an issue that was not within the scope of our *Focus* article[1]. It is a clinically important disease manifestation, yet hardly ever lethal, unlike Chagas cardiomyopathy. It is also true that Hontebeyrie-Joskowicz's paper[2] provided the first evidence of T-cell-mediated autoimmunity in murine models of *Trypanosoma cruzi*-induced denervation. However, the first papers to provide laboratory evidence for autoimmunity in Chagas disease were published in the 1970s, more than 10 years earlier than Hontebeyrie-Joskowicz's publication[2]. Maybe the most compelling of these earlier studies was the identification of effector T cells derived from Chagas cardiomyopathy patients[3] or experimental animals[4] destroying uninfected heart fibers.

Our contention that the experimental *T. cruzi*-infection of the mouse is an inadequate model for chronic Chagas disease pathology in humans comes from the discrepancy between human and murine pathology in chronic infection. Based on the literature and on our own observations[5], we know that chronically infected mice hardly ever (if at all) show signs of an inflammatory dilated cardiomyopathy, a hallmark of symptomatic chronic Chagas disease in humans. Conversely, the incidence and severity of peripheral neurone damage among chronically *T. cruzi*-infected mice (47% of mice showed hindlimb movement abnormality in Hontebeyrie-Joskowicz's report[6]) is without parallel in human chronic Chagas disease. Thus, a belief that is shared among several investigators is that caution must be exercised when extrapolating to human disease findings from murine models of chronic Chagas disease. In this setting, the transfer of neurological clinical signs secondary to demyelination of large peripheral nerves with a T-cell line from an infected mouse is no doubt interesting, but this finding may not have a direct bearing on the pathogenesis of human chronic Chagas disease.

Dr Hontebeyrie-Joskowicz also argues that tissue-damaging T cells have a Th2 profile in chronically *T. cruzi*-infected mice[6]. In order to study the cytokine production by T cells infiltrating heart lesions in human Chagas cardiomyopathy patients, we obtained polyclonal T-cell lines from endomyocardial biopsies taken from ten patients with severe Chagas disease cardiomyopathy, using previously described techniques[7]. The analysis of the cytokine-production pattern upon PHA stimulation of the heart derived T-cell lines from chronic Chagas cardiomyopathy patients indicates a predominance of IFN-γ (the prototype Th1 cytokine), and no trace of IL-4 (the prototype Th2 cytokine) (E. Cunha-Neto *et al.*, unpublished). These results are consistent with a predominantly Th1-driven delayed-type hypersensitivity tissue-damage process in human chronic Chagas disease cardiomyopathy.

As to the identity of the relevant cross-reactive molecules whose recognition could be associated with tissue damage, we did not intend to postulate the myosin-B13 system as the only relevant component for tissue-damaging molecular mimicry in Chagas cardiomyopathy. Rather, we tried to show that, based on objective criteria discussed exhaustively within the *Focus* article[1] (as was molecular definition of autoantigen, organ-specific expression of autoantigen, and association of autoimmune recognition with symptomatic disease), the myosin-B13 system may stand as the most likely candidate among the relatively few molecularly defined antigen systems studied so far.

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Defining Resistance in *Schistosoma*

Although much further research is required, Fallon and colleagues[1] have made a strong case for believing that praziquantel is like other antiparasitic drugs: resistance can develop to it. Their suggestion that resistance be clearly defined is both helpful and timely, but we must be careful to distinguish between the presence of resistance and the degree of resistance. There is also the problem of distinguishing between resistance and tolerance.

As Fallon and colleagues correctly observe, tolerance is an innate insusceptibility of a parasite to a drug, even before the parasite has been exposed to the drug, rendering the drug of little or no practical use, eg. *Schistosoma haematobium* is innately tolerant to oxamniquine.

Tolerance may also be expressed as a stage phenomenon, and exposing an unsusceptible stage of development (eg. the schistosomulum) to the drug would be unlikely to increase the frequency of genes for resistance. However, in some natural populations, there is variation in the numbers of worms with genes for an altered drug target (or worms lacking an activating enzyme, in the case of oxamniquine resistance[2]) before a drug is ever used. This appears to be the situation with *S. mansoni* in East Africa[3]. We would, therefore, suggest a different definition of resistance to that of Fallon and colleagues who define the degree of resistance (a fivefold increase in ED_{50}), rather than resistance *per se*.

We suggest the following definition:

> 'A population of *Schistosoma* is resistant when either a susceptible population shows a significant decrease in its response to a schistosomicide or it is significantly less responsive than a fully susceptible population. The change is due to an increase in the proportion of worms unresponsive to the drug and may be partial or complete. It is complete when the maximum dose of the drug tolerated by the host has no effect on the parasite population. The resistance will be heritable.'

This is a modified version of a definition Coles and Bruce[4] put forward in 1990, which follows the concept of resistance in nematodes[5,6]. With *in vitro* selection[7], it may

be possible to obtain worms that are more resistant to drug therapy than is a fully resistant population *in vivo*, as drug toxicity is not involved. An internationally agreed definition of resistance in *Schistosoma* would help avoid confusion in the future.

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Schistosome Resistance to Praziquantel: Fact or Fiction?

It is with great interest that we read the article by Fallon, Tao, Ismail and Bennett published in a recent issue of *Parasitology Today*[1] and we fully endorse the call for a standard protocol for assessing drug resistance, but we felt that there were some areas that were not addressed. The authors focused largely on the adult worms as the key stage for assessing resistance to a challenge infection; however, it is the eggs which will carry the gene(s) and express the phenotype for resistance. In addition, resistance is unlikely to be present in all eggs, even from a single resistant worm. We[2,3] and others[4] have found that immature eggs in the tissues are not susceptible to praziquantel (PZQ), and the five-day regime, suggested in the protocol, does not effectively address this problem. We would advocate that two doses of PZQ, 15 days apart, is sufficient to allow the immature eggs in the tissue to mature and be killed by the drug. This is also important when assessing egg viability because the authors' protocol calls for the mice to be autopsied, 20 days after the last treatment. During this period, any immature eggs deposited in the tissues prior to when the majority of the worm population was killed by the drug treatment will mature and may therefore give an underestimate of numbers of resistant eggs in these tissues.

For the above reasons, we would suggest the following modifications in the standard protocol. (1) Treat mice with two doses of PZQ, 15 days apart. (2) Following the second dose, check daily (until autopsy) for the presence of eggs in faeces, and carry out the egg-hatch test.

We think that these are important considerations and should be incorporated into any standard protocol or assessment of PZQ resistance in schistosomiasis.

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Book Reviews

Models for Infectious Human Diseases: Their Structure and Relation to Data

edited by Valerie Isham and Graham Medley, Newton Institute and Cambridge University Press, 1996. £45.00 (hbk) (490 pages) ISBN 0 521 45339 9

Tension permeates this book. Although essentially a conference proceedings (it is one of three volumes emerging from the Newton Institute's 1993 Epidemic Models Programme), it is far more interesting than the norm. The conference organizers and the editors managed to get under one roof (and into one volume) theoreticians who use very different approaches to human disease modelling. This apparently generated some heat [at one point it is asserted that there exist mathematicians 'even less serious' than a well-known Oxford theoretician (p. 125)], but the editors claim that one of the legacies of the meeting will be the contacts and collaborative links it spawned. Certainly, this volume emphasizes the gulfs that currently exist.

The heart of the matter is the familiar tension between simplicity and complexity. As Dye puts it, one school of thought is that a model's utility is positively correlated with the number of variables and parameters it contains; the other believes the correlation is negative. What emerges from the juxtaposition of papers in this volume is that it very much depends on the questions you want to ask (eg. understanding fundamental processes versus predicting how long control strategies need to be in place), but both schools evidently still question how good the others' answers are. Somewhat orthogonal to the complexity/simplicity divide is the gulf between the use of statistical models fitted to real data, and the use of dynamical theoretical models, which are usually compared qualitatively against data. For example, patterns of changing CD4 counts in HIV can be treated as a question of better predicting future counts, given past counts (based on stochastic processes) or as a problem of identifying the underlying dynamical phenomena (based on deterministic processes). Again it is clear that these different approaches address rather different types of questions (often description/prediction versus explanation). Many of the participants acknowledged the exciting possibilities greater collaboration would bring, but one senses that most