Histidine-rich protein of *Plasmodium lophurae*

SIR — Ravetch *et al.* have reported some very interesting findings on the primary structure and genomic organization of the histidine-rich protein of *Plasmodium lophurae*[1]. Their observation of the presence of multiple copies of the signal-peptide sequence in the genome of *P. lophurae*, along with the increasing evidence for the presence of histidine-rich sequences in additional malarial polypeptides, pose numerous challenging questions. The fragmentary available information seems to suggest that some related sequences have been conserved through the evolution of apparently functionally different malarial polypeptides.

The recent literature on histidine-rich proteins of malaria parasites has certainly had inconsistencies and can seem confusing to newcomers to the field. This creates all the more reason for factual reporting. Until 1983, the unique and fully characterized histidine-rich protein of *P. lophurae* was referred to as the 'HRP' of *P. lophurae* in all the malarial literature. Although in my publications a clear distinction has been set between HRP and other related polypeptides, there have been several references to undefined histidine-containing malarial polypeptides as 'HRP'.

Perhaps by confusing fact with hypothesis or different histidine-rich polypeptides, Ravetch *et al.* have taken their interesting findings totally out of the context of *P. lophurae*. They cite my paper[2] as their source for the statement that the histidine-rich protein "is located in a membrane-bounded compartment that forms part of the specialized parasite organelles implicated in erythrocyte invasion". Technically, these specialized organelles are the rhoptries of merozoites, the infective forms. However, the facts presented in the paper cited show that the protein was purified from cytoplasmic granules of trophozoite stages of *P. lophurae*[2]. As the parasites develop, the granules increase in number and eventually become segregated inside the residual food vacuole. When the host cells lyse and merozoites are liberated, the granules remain enclosed in the food vacuole which is also released.

These facts offer no grounds for speculating that "if histidine-rich protein becomes a surface molecule of *P. lophurae*, it must be secreted" or "if secretion does occur, it would be followed by disassembly of protein aggregates before association with the parasite surface". As shown in the electron micrograph of my paper, the protein aggregates in the form of electron dense granules while it is within the rough endoplasmic reticulum. Therefore, the logical interpretation of the observed structural features which are characteristic of secretory proteins has to be sought in the context of the synthesis and translocation of the polypeptide within cytoplasmic compartments of the parasite, rather than secretion to the surface. I have described a secretory polypeptide that is related to the histidine-rich protein of *P. lophurae* but it is in another species of malaria. Also, the idea of the possible relationship of a histidine-rich protein to the infection process does originate from my paper entitled 'Does a histidine-rich protein from *Plasmodium lophurae* have a function in merozoite penetration?'[3]. This was published as a hypothesis and has been neither proven nor disproven. I would be delighted to see it proven.

Ravetch *et al.* seem confident of the accuracy of the tandemly repeated sequence. In comparison with the known amino acid composition of the mature polypeptide, the deduced sequence shows significant differences in proline and aspartic acid content. In our hands, the histidine-rich sequences of both genomic and cDNA clones were totally unstable in *Escherichia coli*.

Finally, the statement that "other investigators have been unable to reproduce" my results on the protective effect of the histidine-rich protein cannot be supported by the literature cited. The use of altered experimental protocols does not imply "reproduction".

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Climatic effects of volcanic eruptions

SIR — Major volcanic eruptions in the future will cause, as they have in the past, significant short-term climatic changes, and these changes may have severe social consequences[1-5]. Recent discussions of the climatic effects of volcanic eruptions have emphasized their importance as analogues of the consequences of nuclear war[1,2]. While studies of volcanic eruptions can make an important contribution to assessing the effects of a possible nuclear war, we fear that to use volcanic studies in this way draws attention away from the very serious problems that the eruptions themselves present. A nuclear war remains, fortunately, only a hypothetical possibility. But it is certain that climate-altering volcanic eruptions will take place in the future, although the frequency of these is not well established[6].

The most recent such eruption, that of Tambora 1815, caused widespread disruption to agriculture in North America and Europe, leading to economic crises, famine and outbreaks of disease, whose effects have been summarized by Stommel and Stommel[7]. The stratospheric aerosol loading produced by Tambora was equivalent to a peak optical depth of about 1 (ref. 3). Much the largest effects of historic times appear to have been associated with a volcanic aerosol of unknown provenance of AD 536, calculated to have had an optical depth of about 2.5, which had severe effects on agriculture in the Middle East[4]. Several other historic eruptions have had less severe but still significant effects, notably the Laki eruption of 1783[8].

Since 1815, the world's population has increased many-fold. The continuing famines in the arid and semi-arid regions of northern Africa demonstrate the disastrous human problems that result when relatively minor climatic changes affect marginal areas which are already at or near their maximum sustainable populations. An eruption of the magnitude of Tambora taking place at the present day could have catastrophic effects on agriculture, causing crop failures and shortages world wide, with substantial social and political implications. The fact that the frequency of such large volcanic eruptions may be rather low[3] offers little comfort: a Tambora or even a Toba magnitude eruption could take place tomorrow. Furthermore, the climatic effects of volcanic eruptions are a function of their ability to produce stratospheric aerosols as well as their absolute magnitudes[9,10]. Eruptions smaller than that at Tambora could therefore cause acute problems, especially given the present human pressure on food supplies.

Whilst not wishing to minimize the importance of research on the climatic effects of nuclear war, we suggest that some effort should be diverted from the hypothetical to the inevitable, and that attempts be made to determine the possible climatic and agricultural effects of future large and intermediate magnitude volcanic eruptions. Governments and international agencies might then be in a position to prepare contingency plans capable of dealing with the likely eventualities.

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Scientific Correspondence

Scientific Correspondence is intended to provide a forum in which readers may raise points of a rather technical character which are not provoked by articles or letters previously published (where Matters Arising remains appropriate).