occurs between two complementary forms of the peptide and the MHC heavy chain, a stable complex is formed. An allosteric transition[6] could then be invoked to explain a preferential interaction between these peptide-loaded heavy chains and β_2m. In turn, the binding of the β_2m moiety will further stabilize the peptide/class I complex (of which the spontaneous dissociation is very slow[7]), so allowing the translocation of a peptide-loaded class I/β_2m complex to another cellular compartment. Because of the mass action law, the presence of suitable ligand peptides will then progressively drain out the uncomplexed form of the class I heavy chain.

Other peculiar features can also be explained in standard ways. Thus the apparent irreversibility of the β_2m/class I heavy-chain dissociation[8] may be due to the fact that the association rate, obeying a trimolecular kinetics, may be undetectable in the diluted *in vitro* conditions. Moreover, biosynthetic studies showing that class I heavy chain must associate with β_2m within 30 min of translation[8] may result from a competition with the glycosylation pathway. Thus, even though the mechanism of antigen presentation exhibits unexpected features, there is as yet no need to dig out instructional theories from the fossil records of immunological thinking.

JEAN-MICHEL CLAVERIE
Institut Pasteur Foundation,
28 rue de Docteur Roux,
75724 Paris cedex 15, France

PARHAM REPLIES — In trying to understand antibody specificity, immunologists historically devised various instructional theories. A common theme was the involvement of foreign antigen in forming the three-dimensional structure of antibodies. It is this aspect of instructional models which, I suggested in my News and Views article[2] "A profitable lesson in heresy", had relevance to antigen presentation by MHC molecules, an idea also proposed by J. C. Howard in summing up last year's Cold Spring Harbor symposium. This view is based on a synthesis of many data indicating that under physiological conditions class I MHC molecules do not assemble and get out to the cell surface to stimulate T-cell responses unless they are associated with bound peptides and in appropriate conformations. Thus MHC molecules, unlike antibodies and T-cell receptors, are dependent for their structure and biological function on association with putative antigens.

In Paris, it seems that some are still eager to burn heretics. Claverie accuses me of "defending a surprising instructionalist theory of protein folding" that he believes contradicts the well-established rules of protein folding. In part this is a semantic issue. In saying that "MHC molecules fold up around the peptides they present to T-cell receptors", I meant that peptides contribute to the acquisition of tertiary and quaternary structure and not to formation of basic elements of secondary structure, as apparently understood by Claverie.

More distressing problems exist with Claverie's exposition of what proteins can and cannot do, which appear to stem from reliance on a chemistry text published in 1979 and ignorance of newer results suggesting that protein folding *in vivo* is not necessarily identical to that observed *in vitro*. The dichotomy between protein folding as viewed by the physical chemist and as viewed by the cell biologist has been recently reviewed[9] and it is clear from a spectrum of biological systems that the biosynthesis, membrane translocation and subunit assembly of certain proteins involves molecular chaperones[10] that control their folding and unfolding. Thus, folding of class I MHC heavy chains in the complex environment of the cell need not be spontaneous and faster than chain synthesis, as concluded by Claverie.

The historical debate about antibody specificity was between instruction and selection; the first of these alternatives postulated one primary structure folded under the influence of antigen to give multiple conformations with different combining-site specificities; and the second correctly argued for numerous primary structures from which an antigen could select those with sufficient combining-site affinity. In denouncing instruction for MHC, Claverie turns to its historical foe and claims that "the results of Townsend *et al.* can still be interpreted within the standard selectionist framework". His suggestion that both peptides and class I MHC heavy chains have multiple interconverting conformations, that complexes will form between particular conformations, and that their stabilization may have mass-action effects is reasonable. But surely it is more a kinetic description of instruction — different peptides binding conformations of the same MHC sequence — rather than of selection, with its implication for distinguishing distinctive primary sequences. Claverie appears to have confused selection in the general sense with selection in its specific, immunological sense.

In his last paragraph, Claverie criticizes the suggestion that conformational requirements for bound peptide can explain previously unexplained properties of class I MHC molecules, and implicitly challenges the now widely held belief that bound peptides are essential components of normal, functional class I MHC molecules. Claverie brings no news to this subject and his alternative explanations do nothing to perturb my views. That rate-limiting glycosylation can explain why class I MHC heavy chains must associate with β_2-microglobulin (β_2m) within 30 min of translation is amenable to experiment, and one should perhaps encourage Claverie to test his hypothesis.

In the case of denaturation/renaturation, Claverie's grasp of the data appears tenuous. Our own experiments showed that unfractionated but denatured class I molecules can be efficiently renatured whereas reconstituted class I heavy chains and β_2m cannot; the difference cannot be explained in terms of protein concentrations as they were kept identical. One can also take issue with the suggestion that the association of heavy chain and peptide involves trimolecular kinetics, which I assume means a three-body collision. This is unlikely to be a significant pathway compared to the initial formation of a bimolecular complex followed by binding of the third component — a mechanism in fact mooted by Claverie in his previous paragraph.

Claverie and colleagues have keenly followed Alain Townsend's experiments and have previously developed a "peptidic self" model of the immune system as a "logical generalisation based on an interpretation of results by Townsend *et al.*"[11]. This model emphasized a role for MHC molecules in determining the conformation of antigenic peptides as presented to T cells which perhaps explains Claverie's extraordinary reaction to consideration of the reciprocal effect.

On reading "that such [instructional] theories have vanished from immunology because they do not make much sense at the molecular level", it is worth considering that much of the vigour of immunology has stemmed from the discovery of phenomena such as MHC restriction that did not make much sense within the prevailing molecular framework. Application of molecular biology and new technologies to the study of protein folding and stability is now producing results that significantly challenge both the existing dogma and generalizations based on analysis of small numbers of simplified and model systems[12]. MHC–peptide interactions have unusual features for study and could provide unique contributions to this area.

PETER PARHAM
Department of Cell Biology,
Stanford University School of Medicine,
Stanford, California 94305, USA

1. Townsend, A. *et al. Nature* **340**, 443–448 (1989).
2. Parham, P. *Nature* **340**, 426–428 (1989).
3. Schulz, G.E. & Schirmer, R.H. in *Principles of Protein Structure* (Springer-Verlag, New York, 1979).
4. Bjorkman, P.J. *et al. Nature* **329**, 512–518 (1987).
5. Kourilsky, P. & Claverie, J.M. *Adv. Immun.* **45**, 107–193 (1989).
6. Monod, J. *et al. J. molec. Biol.* **12**, 88–118 (1965).
7. Chen, B.J. & Parham, P. *Nature* **337**, 743–745 (1989).
8. Krangel, M.S., Orr, H.T. & Strominger, J.L. *Cell* **18**, 979–991 (1979).
9. Rothman, J. E. *Cell* **59**, 591–601 (1989).
10. Ellis, R. J. *Nature* **328**, 378–379 (1987).
11. Kourilsky, P., Chaouat, G. Rabourdin-Combe, C. & Claverie, J.-M. *Proc. natn. Acad. Sci U.S.A.* **34**, 3400–3404 (1987).
12. Alber, A. *A. Rev. Biochem.* **58**, 765–798 (1989).