Panel discussion on slow infections¹

Membrane hypothesis of scrapie

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I should like to say just a few words about the membrane hypothesis of scrapie. This hypothesis has not always been clearly understood because it incorporates three distinct but related propositions.

1 The first proposition states that scrapie activity is an integral part of a cell membrane, ie, even if a chemical change in scrapie is confined to a single macromolecular species, this molecule can only infect a new cell as part of a large membrane complex, probably entering by a process of membrane fusion. Infectivity is a property of the whole membrane fragment containing the macromolecule, and this macromolecule will possess no biological activity if isolated in the pure state. It must be emphasized that this first proposition when considered in isolation makes no postulate about the nature of the scrapie agent, only about the way scrapie activity enters a new host cell.

2 The second proposition states that the primary chemical change in scrapie-affected membranes may involve the oligosaccharide chains of glycoprotein molecules.

3 The third proposition, for which various modifications have been put forward, including the linkage substance hypothesis of Adams and Field, makes suggestions about the way in which abnormal membrane structures may be replicated.

There is no time here to go into detail about the nature of the evidence supporting the first proposition, but I have reviewed it in an article shortly to be published in the *Journal of Infectious Diseases*. The weight of this evidence is quite substantial but of course if it is accepted then we are landed with a scrapie situation where we are dealing with a two-component system. This has consequences when considering the second proposition of the membrane hypothesis that we did not fully appreciate ourselves when the hypothesis was first put forward. For instance, many of the apparently unusual physico-chemical properties of the scrapie agent can be ascribed to the membrane carrier and effects on its ability to fuse with the host cell; and some of the

extensive genetic variation among primary sheep isolates may be explicable in terms of the physico-chemical properties and variation of the membrane vehicle rather than as properties of the scrapie agent itself.

However, the exceptionally high 'resistance' of the scrapie agent to ultraviolet light remains to be explained, and there is also a great deal of lesser evidence suggesting that the scrapie agent cannot readily be classed as a virus. The argument is at present very finely balanced, and the scrapie agent may yet turn out to be a type of small viroid as suggested by Diener, even though the scrapie position is clearly distinct from the simpler situation which is apparent in potato spindle disease. On the other hand, the best alternative possibility is still perhaps that embodied in the second proposition of the membrane hypothesis. The fascinating controversy can only be resolved by the positive identification of the physical and chemical modifications that confer scrapie activity on a biological membrane.

Systems of virus survival

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Between the host-virus relationships with which the meeting was introduced and the basic clearing mechanisms with which it ended, there appears a variety of methods by which viruses manage to persist in infected animals. Some overlap between systems occurs because one or other of the two predominant questions, 'How does the virus avoid being eliminated?' and 'How does it cause disease?' may have the same answer in different systems.

Balanced Cytopathic Infections

Balanced cytopathic infections exist, well exemplified by persistent adenovirus infection, involve few cells at any one time but do not give rise to chronic disease, nor, apparently, to recurrent acute lesions.

¹No attempt has been made to record the discussion in detail but the contributions from some members of the panel are presented in conclusion.