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.

Delayed Cytopathic Infections

A prolonged state of balance is evident with two cytopathic viruses, visna commonly, and measles virus rarely, when it produces subacute sclerosing panencephalitis. In the one, prolongation must be attributed to the character of the virus; in the other, prolongation is more likely to be characteristic of the patient or of the circumstances of infection. The clue to persistence may be found in the next system where the viruses are less virulent.

Regulated Productive Infections

The main question for viruses which have no cytopathogenic effect or a greatly delayed effect, but which are antigenic, is how they evade host defences. Immune tolerance is often invoked, though not often analysed but the clearest factor in the group, lymphocytic choriomeningitis, Aleutian disease of mink, lactic dehydrogenase increase and infectious anaemia of horses, is the formation of much non-neutralizing antibody. Its protective effect on free viruses and on virus-producing cells could well bear much more investigation and may apply in the previous system, for neutralizing antibody is simultaneously present. Disease seems to be a secondary phenomenon here, produced by immune complexes or by cell-mediated immunity. Leukaemic or tumour-forming agents may be similarly protected from the host, but other mechanisms appear, as seen in the system of regulated incomplete infections.

Alternating Infectious States

Certain viruses alternate between productive infection, which is cytopathic, immunogenic, and, indeed, controlled by normal immune responses, and non-productive infection which avoids immune rejection by making no accessible antigens. This is well seen with virus of the herpes group, *Herpes simplex* and *Herpes zoster*. The non-productive stage seems to take place in sensory ganglia in the central nervous system. How the virus is integrated with the cell and what controls reactivation is not known, but cells with little DNA turnover may be a suitable refuge for a lonely virus DNA.

Regulated Incomplete Infections

Partially productive infection seems to be characteristic of tumour-inducing and leukaemic viruses and again the herpes group illustrates this well in Marek's disease and in Lucké renal carcinoma. The immune response against virus-induced tumour antigen is either not powerful or is masked in some way, but the switch between the fully productive and

partially productive state is open to investigation being subject to temperature control. It would be strange if a naturally occurring virus were, so to speak, a temperature-sensitive mutant! Partially productive infections may also influence immune processes themselves, as in glandular fever and virus lymphomas, but why is cytomegalovirus so inert?

Non-immunogenic Infections

The unidentified agents of kuru, Creutzfeldt-Jacob disease, and scrapie are cytopathic, but completely non-antigenic. They are thus at the opposite end of the range from non-cytopathic immunizing viruses and need no protection against mechanisms which they do not provoke. Whether they destroy brain cells primarily or secondarily remains to be discovered.

Some general features were alluded to which merit discussion or investigation.

1 A long evolutionary relationship between host and virus is implied by the strong species-specificity of the viruses, and the concomitant difficulty, even when transfer to another host is possible, of finding a model of the disease.

2 It was felt by some that ability of a virus to grow in macrophages or leucocytes might decide the balance of events. Here stress should be placed rather on persistence in these cells, since acutely cytopathic viruses frequently grow in the same types of cells, eg, pox viruses, measles virus, arboviruses. In these sites virus replication might well suppress immunological responses. In this connexion it should also be added that many persistent viruses do not induce the formation of interferon, a point not discussed by any speaker.

3 Immunological immaturity is strongly related to the outcome of infection. Non-neutralizing antibody appears in some slow diseases naturally and also forms when immuno-suppressed animals are deliberately infected. The lack of antibody balance thus induced may be recovered from very gradually, as in congenital infection with rubella virus. Other immune responses may be defective besides antibody production.

4 The conception of a target organ appeared from time to time. The great amount of feline leukaemia virus in respiratory epithelium raises the question of whether, in prolonged disease, the affected organ is the true reservoir of virus. Are stem cells of leukaemic marrow and thymus the only source of virus? Where is the origin of hepatitis virus in the carrier patient who has recovered from jaundice? What of the brain in scrapie when in fact the spleen may be full of virus? Could multiple sclerosis be due to virus infection elsewhere than in the brain?