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Mims C. A. Aspects of the pathogenesis of virus diseases.
Bacteriol. Rev. 28:30-71, 1964.

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The paper surveys what was known in 1964 of the pathogenesis of virus infections and also describes original work not published elsewhere. Topics include the role of reticuloendothelial macrophages in the maintenance of viraemia and in control of viral access to hepatic cells. The spread of viruses in lymphoid tissues and in other organs is analysed at the histological level using the fluorescent antibody technique. [The *SCI*® indicates that this paper has been cited in over 435 publications.]

Early Studies of Mechanisms in Viral Pathogenicity

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The paper appeared in a review journal but it contains many experimental observations that I might have built into separate research papers. At that time the subject of the pathogenesis of virus infections was limping along beside regular virology, relatively neglected. Yet the understanding of mechanisms in virus pathology and disease seemed of immense importance, and the topic was moving into a new era away from mere descriptions of histopathology. I had been taking a quantitative analytical approach and making use of the fluorescent antibody technique developed by Dr. A.H. Coons, which enabled one to identify individual infected cells in tissues.

As an enthusiast, I was dismayed by the many fine research workers who shied away from studies of pathogenesis. To them it was an imprecise, messy field of investigation and they retreated with relief to their cleaner *in vitro* experiments, where conditions were controllable and results more easily interpreted. The paper surveyed what little was known at the time, and my own results were interwoven into the text. These included a brief study of

the cell to cell spread of ectromelia virus through the lymphoid tissues of mice and the demonstration that when rats drank water containing phage particles, the latter appeared in thoracic duct lymph within minutes. There were more lengthy studies of viraemia and its control by reticuloendothelial cells, the role of Kupffer cells as gateways to hepatic cells, and the excretion of viruses into bile.

I wrote the paper while at the John Curtin School of Medical Research in Canberra, Australia, at that time in its heyday, under Professor Frank Fenner. It was a magnificent environment for a young scientist, exposed to future research giants including J. Cairns, S. Fazekas, W.K. Joklik, W.G. Laver, and many others. But in this paper, as in my earlier experimental work both in Uganda and in Canberra, I was very lucky to have John Cairns as a close friend and colleague. I was inescapably influenced by his wise counselling, critical comments, and suggestions, all given so gently and unselfishly.

Becoming immersed in the subject of pathogenesis may have had something to do with my initial degree and background in zoology at University College London before starting at medical school. As an ardent admirer of parasites, I used to imagine myself as a microorganism inside a hostile host, trying to survive and trying to get round those formidable host barriers and defences. Therefore the research questions I asked were—Which actual cells does this virus infect? How does it get to them? How does it spread through organs and to other parts of the body? How does it avoid being phagocytosed and killed? This approach was in later years, after coming to Guy's Hospital, London, expanded and systematised in a little book,¹ which has probably had more of an impact than the 1964 paper, and I used the same approach to viruses and the immune system.²

Perhaps the 1964 paper is quoted not only because it was a review and a collection of experimental results, but also because it encouraged many virologists to enter an exciting and neglected field of research. Nowadays, molecular biologists are pinpointing segments of the viral genome associated with virulence. But even when viral gene products are characterised, it may be a difficult step to understand their mode of action *in vivo*. Continued attention to pathogenesis is essential if the full fruits of the molecular biological revolution are to be enjoyed.

1. Mims C. A. *The pathogenesis of infectious disease*. London: Academic Press, (1976) 1987. 342 p. (Cited 75 times.)
2. ————. Interactions of viruses with the immune system. *Clin. Exp. Immunol.* 66:1-16, 1986. (Cited 15 times.)

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