

# Seeing the Previously Invisible

HERPESVIRUSES HAVE INFECTED animals for millions of years, pre-dating the evolution of mammals, and then humans.<sup>1</sup> Throughout this vast time-scale they have progressively adapted to persist, despite our acquisition of innate, humoral and cell-mediated immune responses. By learning to prevent/reduce/abrogate specific immunity, herpesviruses can replicate and transmit to other individuals.<sup>2</sup> This ensures their survival in each species but without necessarily declaring their presence by the production of disease.<sup>3</sup>

Little more than a decade ago, humans were thought to harbour only five herpesviruses. With the advent of methods to culture peripheral blood mononuclear cells and the technique of representational difference analysis, another three human herpesviruses have been added to the list.<sup>4-6</sup> This issue of *HERPES* concerns two of these: human herpesvirus 6 (HHV-6) and human herpesvirus 7 (HHV-7).

## HHV-6 and HHV-7 and Specific Clinical Diseases

Now that laboratory methods exist to detect these viruses, quantitate their viral loads in body fluids,<sup>7,8</sup> and measure past exposure to infection by detection of immunoglobulin G antibodies (see *The Biology and Natural History of Two Emerging Pathogens, Human Herpesvirus 6 and Human Herpesvirus 7* by Alessandra Stefan *et al.*, pages 78–81), it is possible to ask whether infection causes particular clinical diseases or syndromes.

The childhood illness 'exanthem subitum' is so named because of the sudden onset of the rash and rapid ending of the high fever (see *Exanthem Subitum [Roseola Infantum]* by Caroline Breese Hall and Mary Caserta, pages 64–67). Paediatricians had often thought exanthem subitum was an infectious disease, and this was confirmed in 1950 when the illness was experimentally transmitted to another human neonate.<sup>9</sup> In 1994, Yamanishi and colleagues reported HHV-6 seroconversion and culture of virus in 4/4 cases of exanthem subitum.<sup>10</sup> It was shown subsequently that primary HHV-6 infection can cause high fever in the absence of a rash and that HHV-6 was a major cause of febrile fits.<sup>11</sup>

## The Neurotropism of HHV-6

The availability of specific laboratory tests has thus revealed a strong association between HHV-6 and medical conditions of previously unknown but presumed infectious aetiology. These techniques have therefore shed light on the pathogenesis of HHV-6, allowing the previously invisible aetiological link to be seen, and also clearly documented the neurotropism<sup>12</sup> of the virus. Subsequent studies showed HHV-6 to be associated with acute focal encephalitis (see *Neuroinvasion of Human Herpesviruses 6 and 7* by David Kimberlin, pages 60–63).<sup>13</sup> Could these techniques be used further to provide an aetiology for medical conditions not previously accepted as having an infectious component, such as multiple sclerosis (MS)?



Paul Griffiths

In the past, many infectious agents have been proposed, but not confirmed, as candidates for the cause of MS, an autoimmune demyelinating disease. In this issue, Duncan Clark reviews the evidence associating *Human Herpesvirus 6 and Multiple Sclerosis*, (pages 73–77). It is clear that a herpesvirus persisting in oligodendrocytes and reactivating periodically represents a strong potential candidate trigger for the immunopathological demyelinating response of MS. Yet, the studies performed to date, while providing some tantalizing suggestive information, fall far short of proving the veracity of the proposed association.

Specifically, the demonstrated neurotropism of HHV-6 urges caution when interpreting its presence in the central nervous system of a condition not proven to have an infectious aetiology. Owing to the need for more effective therapies in MS, studies must continue into the possible MS/HHV-6 association, and the results of further placebo-controlled trials of prophylaxis with anti-herpes compounds<sup>14</sup> are awaited with interest, since these represent a practical way of demonstrating that a herpesvirus may be one of several triggers of the complex disease processes that culminate in clinical MS.

## Note: New Feature for *HERPES*

This issue of *HERPES* sees the launch of a new *Letters to the Editors* section, with contributions from Zane Brown and Tom Weber (pages 82–83). Letters related to the contents of *HERPES* or to herpesvirus infections are welcome, and readers are encouraged to correspond via this new page.

Letters concerning an article in *HERPES* must be received within 2 months of its publication. Decisions regarding publication of correspondence will be based on timeliness, interest to the readers of *HERPES* and space available. Letters may be submitted on disk or via e-mail, c/o the Publishing Editor at the Editorial Office address shown on the inside front cover of this issue.

## REFERENCES

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