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Arboviruses causing human disease in the Australasian zoogeographic region*

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Summary. Over 65 arboviruses have been reported from countries in the Australasian zoogeographic region, but only a few have been implicated in human disease. These include the flaviviruses Murray Valley encephalitis (MVE), Kunjin (KUN), Kokobera (KOK), and dengue, particularly types 1 and 2; the alphaviruses Ross River (RR), Barmah Forest (BF), and Sindbis (SIN); and the bunyaviruses, Gan Gan and Trubanaman. In this paper recent epidemiological and clinical results pertaining to these viruses are reviewed, with major emphasis on MVE and RR viruses. The extensive early studies of Australian arboviruses have been reviewed by Doherty [49, 50], and their ecology and vectors more recently by Kay and Standfast [87]. In addition, the biology of MVE and KUN [113] and RR [87, 114] viruses have been the subjects of more detailed reviews.

The Australasian zoogeographic region is defined as countries east of the Wallace and Weber lines, two hypothetical lines in the Indo-Australian archipelago where the fauna of the Australasian and Oriental regions meet. Seroepidemiological studies of human arboviral infections have suggested that the Japanese encephalitis flavivirus and the chikungunya alphavirus occur only in the Oriental region, whereas the related MVE and RR viruses, respectively, are restricted to the Australasian region [85, 148]. Serological results from Wallacea, the zone between the Wallace and Weber lines, are not so clear-cut [85]. This review is therefore restricted to countries east of Wallacea, specifically New Guinea and Australia.

Flaviviruses

Murray Valley encephalitis virus

The major aetiological agent of Australian encephalitis, MVE virus, occurs in Australia, Papua New Guinea, and probably islands in the eastern part of the Indonesian archipelago.

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It has recently been the subject of an extensive review by Marshall [113]. Epidemics of severe, highly lethal encephalitis had occurred in Eastern Australia in 1917, 1918, 1922 and 1925, and had been given the name Australian X disease. A further epidemic occurred in the Murray Valley area of south-eastern Australia in 1950–51, during which the virus was isolated for the first time from the brains of 4 deceased patients [71, 121], and given the name Murray Valley encephalitis virus. Sporadic cases were then diagnosed in 1956 and 1971 in eastern Australia, with the most recent major epidemic occurring in 1974. The clinical aspects of the encephalitis have been described for the 1951 [135] and 1974 [10] epidemics. In the 1951 epidemic 19/45 (42%) reported cases were fatal [5] compared with 13/58 (22%) in 1974 [69]; artificial respiration has been applied during the last epidemic, otherwise this figure might have been higher. Two cases of encephalitis due to MVE have also been reported from New Guinea in 1956 [72] and 1960 [65]. The former was a fatal case in a 14 year old boy from Papua, the latter a serologically confirmed case from Dutch New Guinea (Irian Jaya) who exhibited features of Parkinsonism when reviewed 4 months after hospitalisation.

Since 1974, 44 cases of Australian encephalitis due to MVE have been reported from northern Australia, of which 28 occurred in the north of Western Australia, 13 in the Northern Territory, and 3 in Queensland ([107, 110, 145]; D. Smith, J. Burrow, B. Currie, A. K. Broom and J. S. Mackenzie, unpubl. obs.). Six of the Western Australian cases and two cases from the Northern Territory were fatal. Most serious cases were in Aboriginal infants, which indicated that disease resulting from exposure early in life was more likely to be severe. A marked male predominance was observed in cases involving Aboriginal children [110]. Seroepidemiological studies have shown a high incidence of subclinical infections in certain Aboriginal communities in northern Australia, with $\geq 90\%$ of the children seroconverting to MVE by the age of 10 ([48, 95]; N. King, A. K. Broom and J. S. Mackenzie, unpubl. res). These studies have suggested that only 1 in about 1000 infections results in clinical disease, although in some outbreaks in epidemic areas higher infection rates may occur. It is unknown whether the low case/seroconversion rates are due to variations in susceptibility, virus virulence or both. Thus far, genetic studies of isolates from human cases and mosquitoes have not revealed any consistent differences. Mouse experiments with monoclonal antibody escape mutants of MVE have indicated that a single amino acid change in the E gene product might be responsible for altering the virulence phenotype [106]; genetic studies have not been sensitive enough to investigate this issue thoroughly. However, since a field isolate of low virulence did not share the amino acid change in the E protein of the avirulent monoclonal antibody escape mutants (R. J. Coelen and J. S. Mackenzie, unpubl. res.), the issue of virulence requires further study, e.g. by making use of an infectious clone of MVE.

A large number of studies has been directed at determining the major vertebrate hosts of MVE. Waterbirds may be the major hosts, particularly members of the order Ciconiiformes, although members of other avian orders and certain domestic and wild animals have been implicated on serological grounds. MVE has been isolated from the white-faced heron (*Ardea novaehollandiae*) [116], and in seroepidemiological surveys the highest antibody incidence has been found in the rufous night heron (formerly the nankeen night heron *Nycticorax caledonicus*). This species has also been shown to be particularly susceptible to experimental MVE infection [16, 17].

The first mosquito isolates of MVE were obtained from *Culex annulirostris* trapped at

Kowanyama (Mitchell River Mission) in Northern Queensland in 1960 [57]. Subsequent field studies have confirmed that *Cx. annulirostris* is the major vector of MVE in Australia, accounting for > 90% of all isolates. Virus carriage rates may be high during epidemics; the figure for MVE and KUN during the 1974 epidemic in south-east Australia was approximately 1 : 950 [116], whereas in the north-east of Western Australia, carriage rates of > 1: 91 have been recorded during small outbreaks [23, 24]. MVE has been occasionally isolated from a number of other mosquito species, including *Aedes normanensis* [23, 25, 57], *Ae. pseudonormanensis* [24], *Ae. eidsvoldensis* (*), *Anopheles annulipes* [23], *Anopheles bancroftii* (*), *Cx. quinquefasciatus* (*, [94]) Cx. *australicus* [116], *Cx. palpalis* (*) and *Mansonia uniformis* (all asterisks: A. K. Broom, M. D. Lindsay, A. Wright and J. S. Mackenzie, unpubl. res.), but the vector competence of these species and their role in transmission cycles has still to be determined. Only *Cx. quinquefasciatus* has been shown experimentally to transmit MVE [117]. In the north of Western Australia, MVE has been isolated from mosquitoes more frequently than KUN virus, the ratio being approximately 4 : 1, whereas in northern and southern Queensland and south-east Australia, the opposite has been found, with isolation rates from *Cx. annulirostris* of 1 : 3 [113]. Marshall [113] speculated that MVE (and KUN) may survive through dry season periods by vertical transmission in the desiccation-resistant eggs of certain *Aedes spp.*; the isolation of MVE from *Ae. normanensis*, a floodwater breeding species with desiccation-resistant eggs lends credence to this hypothesis [23, 25]. Recently, MVE virus was isolated from field-caught male Aedes (Macleaya) species mosquitoes trapped soon after the first wet season rains in the East Kimberley (A. K. Broom, M. D. Lindsay, C. A. Johansen, A. E. Wright and J. S. Mackenzie, unpubl. res.), thus providing further evidence for vertical transmission as a mechanism of persistence of the virus.

Considerable evidence has accumulated to suggest that the only known enzootic area of MVE activity in Australia is the Kimberley region of Western Australia. Thus, virus can be isolated from mosquitoes in most months of the year [24, 94, 96], and seroconversions occur annually in sentinel chicken flocks [18, 21, 22, 24]. MVE may also be enzootic in the Northern Territory, but only a single isolation of MVE has been obtained [152] despite extensive mosquito collections; 13 cases of Australian encephalitis have been reported since 1978 ([107, 145]; D. Smith, J. Burrow, B. Currie, A. K. Broom and J. S. Mackenzie, unpubl. res.), and serological testing of sentinel chicken flocks from January 1992 has indicated MVE activity at several locations in 1992 [3, 19, 20], and 1993 [21]. The endemicity of MVE in northern Queensland is also uncertain. Although the virus was first isolated in north Queensland [57], and many seroconversions have been reported in certain Aboriginal communities [48, 60], few isolations have been made from mosquitoes despite collections particularly between 1960 and 1980, and only occasional cases of Australian encephalitis have occurred. However, seroconversions in sentinel chickens were observed at Kowanyama [60, 61], and in a study carried out in the Flinders River basin between 1974 and 1977, MVE (and KUN) activity was observed in each year [90]. Earlier seroepidemiological studies of man and animals have indicated that MVE activity might be widespread in Queensland [49]. Thus the paucity of virus isolations from mosquitoes trapped in Queensland and the Northern Territory is surprising. MVE activity occurs occasionally in the Pilbara region of Western Australia as demonstrated by sporadic cases of Australian encephalitis [110], and by virus isolations from mosquitoes and seroconversions in sentinel chicken flocks [19, 21, 24]. There has been no incidence of

MVE activity in south-east Australia; particularly in the Murray-Darling river basin, since the 1974 epidemic; regular monitoring through mosquito collections and sentinel chicken flocks has been performed, and no evidence of human infections has been detected in seroepidemiological surveys [84]. The rare occurrence of MVE epidemics in south-east Australia may therefore be due to the re-introduction of virus from an enzootic reservoir in northern Australia. Virus movement from the enzootic north tends to follow periods of high rainfall and flooding [6, 69, 120, 126], possibly associated with the movement of infected birds from tropical areas [69, 120]. However, despite the fact that surveillance and monitoring data have failed to prove the presence of MVE in the south-east of Australia during non-epidemic years, cryptic foci of virus activity, as suggested by Marshall [111, 113], may still exist. In New Guinea, a high prevalence of antibodies to MVE has been found in the lowlands and coastal regions (e.g. [85, 154]; R. Hawkes, cited in [113]), and it is surprising that more cases of Australian encephalitis have not been observed. This may be due largely to the paucity of diagnostic laboratory facilities and to the high incidence of malaria, with cases of encephalitis misdiagnosed as cerebral malaria.

All MVE virus isolates, regardless of the year of isolation, their geographic or host origin are antigenically closely related and cannot be distinguished by standard serological techniques. Molecular epidemiological studies have been undertaken to investigate the possible genetic divergence between them. It was hoped that such studies would provide information on viral evolution, virulence and virus movement.

Nine MVE virus strains isolated from different areas of Australia between 1972 and 1974, and two strains from Papua New Guinea (PNG) were compared to the 1951 prototype MVE strain by restriction enzyme analysis using Hae III and Taq I restriction enzymes. The Australian isolates all showed similar profiles with a sequence divergence of $< 1.5\%$ and no evidence of systematic genetic drift. In contrast, the two PNG isolates from southern Papua and northern New Guinea generated very different profiles from the Australian isolates and from each other. The genetic divergence between the two PNG isolates was estimated at approximately 6%, whereas the divergence between either PNG isolate and the Australian strains was $> 6\%$ [103]. These findings were extended in a subsequent study using nucleotide sequence analysis. The entire genome of MVE 1951 prototype strain having been sequenced [46, 92], the E gene of nine Australian isolates from three fatal human cases, a heron, and from mosquitoes collected in different locations between 1960 and 1975, and the two PNG isolates, were compared [104]. The nucleotide sequence divergence between any pair of Australian isolates was found to be $< 1.7\%$, and the data suggested that the genotypes of isolates from different regions of Australia change slowly over time but do not diverge independently. The two PNG isolates exhibited 6.8% sequence divergence between each other, and between 10% and 9.3% divergence from the 1951 prototype Australian isolate, indicating that two independent foci of MVE were evolving in PNG. Most nucleotide changes were silent third base substitutions.

In another series of studies, genetic variation among 29 isolates of MVE was investigated using RNase T1 oligonucleotide fingerprinting, restriction enzyme analysis and RNA sequencing [30, 33, 91, 108]. Using an ultra-thin gel development of the RNase T1 fingerprint technique [32], 19 Australian isolates of MVE collected from different geographic regions between 1960 and 1984 and the two PNG isolates were compared. The results support those of Lobigs et al. [103, 104] and demonstrated that the Australian isolates are similar, with a nucleotide divergence of $< 2\%$, while the two PNG isolates are

substantially different from each other and from the Australian isolates [30]. However, the OR156 isolate from the north-west of Australia also exhibited substantial nucleotide divergence from the others. Analysis of a 400 nucleotide region of the NS1 gene and restriction enzyme mapping of 22 Australian isolates from different locations collected between 1951 and 1984 have confirmed the genetic homogeneity of Australian MVE isolates, with the exception of OR156 and of the divergent sequences exhibited by the two PNG isolates [91]. The Australian isolates had a nucleotide divergence in this region of < 1.8%, but OR156 exhibited a 9.3% divergence from the other Australian isolates. The two PNG isolates differed from each other by 4%, from OR156 by 7.2%, and from the Australian isolates by 6.5% nucleotide divergence. The significant divergence of the two PNG isolates and OR156 from the Australian isolates was also apparent in the highly conserved 5' non-coding region. The two PNG isolates were found to contain one extra uridine residue, nominally positioned after nucleotide 54, and OR156 contained two additional uridine residues at this site, which were absent in eight other Australian isolates [31]. In addition, these isolates could be differentiated from all Australian MVE isolates in monoclonal antibody binding studies by their lack of one epitope [77].

A comparison of sequence data from the E [104] and NS1 [91] genes indicated that nucleotide divergence is slow and uniform at any time in widely separated regions of Australia, but the genotypes do not diverge independently. Identical base substitutions have occurred in all MVE isolates obtained after 1971. Indeed, 12 such changes can be identified in the E and NS1 genes of these isolates with respect to the 1951 prototype and the 1960 mosquito isolate. The paucity of Australian isolates prior to 1972 makes it dangerous to speculate, but the data suggest that all isolates from 1972 onwards may have a common progenitor; this provides further credence to the concept that viruses move from enzootic to epidemic areas [108].

Thus only one MVE virus topotype exists in Australia, although three divergent isolates could be distinguished, two from PNG, and one spurious isolate from the north-west of Western Australia. The genotypic and phenotypic characteristics of this latter virus would suggest that it has been imported from PNG or the Indonesian Archipelago. The three divergent isolates indicate that separately evolving genotypes occur outside the Australian mainland, and may represent additional topotypes. The genotypic distribution pattern of MVE differs from those of other flaviviruses, particularly of other members in the same antigenic subgroup, Japanese encephalitis and St. Louis encephalitis, in that a single topotype extends throughout tropical Australia as a single large circulating pool, with the occasional brief introduction into epidemic areas. Indeed, the apparent genetic homogeneity of MVE provides circumstantial evidence against the occurrence of cryptic foci of virus activity in south-east Australia.

Kunjin virus

KUN virus is closely related to MVE virus, both being members of the Japanese encephalitis serological complex of flaviviruses; genome sequence comparisons suggest that it is more closely related to West Nile virus, another member of the complex [34]. Nevertheless, MVE and KUN share a number of biological and epidemiological characteristics [113]. Although KUN also causes encephalitis, the disease is less common and generally milder than that following MVE virus infection [110]. The first case of KUN encephalitis was reported during a small outbreak in Western Australia in 1978 [26, 110]. In an earlier report,

KUN had already been implicated retrospectively as the causative agent of encephalitis in a few cases from the last major epidemic in 1974 [55]. Two further cases have been reported in Victoria in 1984 [125] and Western Australia in 1991 [107, 110], the latter being very mild. KUN has also been associated with non-encephalitic illness with fever and malaise, and sometimes also joint involvement. Cases have been reported from eastern Australia over the past eight years, indicating that this may be a more frequent disease syndrome (e.g. [35, 93]). KUN has also been isolated from a horse with encephalomyelitis [9].

In Australia, KUN virus was first isolated from *Cx. annulirostris* mosquitoes trapped in Northern Queensland at the same location and over the same period as the first mosquito isolation of MVE [57]. As with MVE, the major vector is *Cx. annulirostris*; the main vertebrate hosts are probably members of the order Ciconiiformes, as supported by experimental evidence [16, 17]. Also KUN virus has been isolated from other mosquitoes including *Ae. tremulus* [94], *Cx. australicus* [111], *Cx. squamosus* [60], and *Cx. quinquefasciatus* [54]. Unconfirmed isolations were reported from *An. bancroftii*, *An. farauti* and *Cx. pullus* [60].

The incidence of seroconversions in certain Aboriginal communities and sentinel chicken flocks, and virus isolations from wild-caught mosquitoes suggest that KUN is enzootic across most of northern Australia [20, 24, 48, 60, 96]. However, the epidemiological pattern of KUN differs significantly from that of MVE. As can be concluded from seroconversions of sentinel chickens, KUN is active almost every year in the Pilbara region of Western Australia [e.g. 19, 21, 24] and in occasional inter-epidemic years in south-east Australia [83, 84, 93, 125, 139]. This would suggest that KUN moves more readily than MVE from enzootic to epidemic areas, despite apparently sharing major vector and vertebrate host species, and is more readily dispersed from cryptic foci or perhaps more readily maintained in mosquito cycles through vertical transmission. KUN has not been found in PNG, although antibodies were found in children in the Sepik area (R. A. Hawkes, cited in [113]), but three isolations were made from *Cx. pseudovishnui* collected in Sarawak, Borneo, in the oriental zoogeographic zone [15].

Molecular epidemiological studies were undertaken with 15 KUN isolates collected from different geographical areas over a 24 year period, using restriction enzyme mapping with Hae III and Taq I [105]. All isolates were genetically similar, with an estimed nucleotide divergence of $< 1\%$. Similar results were obtained using RNase T1 oligonucleotide fingerprinting with 22 KUN isolates [68]. The maximum nucleotide divergence was estimated to be 1.5%, and no association was detected between geographic region or host from which the virus was isolated, nor was there any evidence of systematic drift. Like MVE, KUN exists throughout Australia as a single topotype of genetically homogeneous viruses.

All KUN isolates, like MVE isolates, are closely related antigenically and cannot be distinguished by standard serological techniques. However, recent studies with a panel of six monoclonal antibodies produced to the OR393 strain demonstrated antigenic variation in the envelope protein. Ten out of 33 isolates failed to react with all six monoclonal antibodies in an immunoperoxidase assay indicating that at least 2 antigenic types exist in Australia; a different reaction pattern was observed with a KUN isolate from Sarawak that may represent a third antigenic type (C. Adams, R. Hall, A. K. Broom and J. S. Mackenzie, unpubl. res). Further evidence of phenotypic variation has been demonstrated by glycosylation studies. While the envelope protein of the sequenced KUN strain MRM61C

[34] is unglycosylated [158], endoglycosidase F digests of 32 KUN virus isolates indicate that most (20/32) are glycosylated. There is also evidence of biological variation, with some strains producing characteristic syncytia in C6/36 cells that are not observed in cultures infected with other isolates. An initial analysis of these data did not reveal any correlation between these phenotypic variations. However, sequencing of the E gene of selected strains and further analysis of the results with reference to the date, location and source of isolation and passage history may reveal the significance of these changes.

Kokobera virus

Like MVE and KUN, KOK virus also belongs to the Japanese encephalitis serological subgroup of flaviviruses. The virus was first isolated from *Cx. annulirostris* mosquitoes trapped in northern Queensland at the same location and over the same period as the initial isolations of MVE and KUN [57]. Subsequent isolates were obtained from *Cx. annulirostris* mosquitoes trapped in Queensland [60], Western Australia ([96]; A. K. Broom, M. D. Lindsay, A. Wright and J. S. Mackenzie, unpubl. res.) and New South Wales, with isolations also reported from a mixed pool of *Aedes spp.* in PNG (I. D. Marshall, pers. comm.), and from *Ae. vigilax* in Queensland [58]. On serological grounds, the vertebrate hosts of KOK are believed to be macropods, although horses may play a minor role [56, 58].

Seroepidemiological surveys in Queensland [56], PNG (R. A. Hawkes, cited in [113] and New South Wales [83, 84] hinted that occasional human infections occur. This was confirmed in three patients with an acute polyarticular disease from New South Wales and Victoria [11]; two further cases have been reported from Rockhampton in Queensland [37, 42].

Dengue virus

Although dengue was not uncommon in northern Australia earlier this century, with epidemics reported in Queensland, Northern Territory and New South Wales, it disappeared following a dengue type 3 epidemic in north-east Queensland between 1953 and 1955 [47, 59] and did not reappear until March 1981. A large outbreak of dengue type 1 occurred between March 1981 and September 1982 in northern Queensland with several hundred serologically confirmed cases from Cairns, Townsville and Thursday Island [76, 89]; further cases occurred in 1990–1991 in northern Queensland [36, 38, 39]. This was followed in 1992–1993 by a large outbreak of dengue type 2 with > 900 cases confirmed serologically and an additional 950 cases inferred on clinical grounds between March 1992 and June 1993 ([42, 132, 137]; M. Pearce and J. Sheridan, pers. comm.). Most cases have occurred in Townsville and Charters Towers. A single case of dengue haemorrhagic fever was reported from Charters Towers in March 1993 [137]. It is interesting to note that the first case of dengue haemorrhagic fever was recorded in northern Queensland in 1898 [79]. The only vector of dengue in Australia, *Ae. aegypti*, is confined to areas in northern Queensland. Its actual range is unknown, but it has been found as far west as Mount Isa, near the Northern Territory border (P. Whelan, pers. comm.), and there is considerable concern that it may spread across tropical areas of Australia. The available evidence suggests that dengue is not endemic in Australia, and that epidemics arise from virus introduced by viraemic travellers.

Occasional outbreaks of dengue fever have been reported from PNG. The first isolates were obtained from soldiers who became ill in PNG, India and Hawaii during World War II [141]. Of four PNG isolates, one was subsequently classified as dengue type 1, three as dengue type 2; one of the latter was designated as the prototype strain of dengue type 2, New Guinea-C. The first major epidemic to be described occurred in Rabaul in 1971 [159], with > 1100 cases due to dengue type 2. Clinical cases of dengue have been reported, particularly in expatriates from Wewak, Lae, Port Moresby and Madang, but most cases were not confirmed by laboratory diagnosis. *Ae. aegypti* mosquitoes are relatively common in urban coastal areas (R. Sanders, pers. comm.)

Other flaviviruses

Three other Australian flaviviruses have been implicated in human infection from either seroepidemiological studies or putative cases; Alfuy and Stratford, two additional members of the Japanese encephalitis serological complex, and Edge Hill, a member of the Uganda S serological group. Sepik virus, a flavivirus from PNG, has also been suggested as a potential human pathogen.

Alfuy virus was first isolated from serum of a swamp pheasant (*Centropus phasianinus*) [153] and from *Aedeomyia catasticta* mosquitoes [60] trapped at Kowanyama (Mitchell River Mission) in northern Queensland (the same study area as the initial mosquito isolations of MVE, KUN and KOK viruses). It was subsequently isolated from *Cx. pullus* in Queensland [50] and *Cx. annulirostris* in Western Australia (A. K. Broom, R. A. Hall, M. D. Lindsay, A. Wright, J. S. Mackenzie, unpubl. res.). The vertebrate hosts for Alfuy virus are believed to be wild birds [153]. A seroepidemiological survey carried out in New South Wales indicated that human infections may occur [83], and there has been an unconfirmed report of a case of mild polyarticular disease attributed to Alfuy virus [8].

Stratford virus was first isolated from *Ae. vigilax* mosquitoes trapped at Cairns, northern Queensland, in 1961 [57]. A subsequent isolate was obtained from a mixed pool of female mosquitoes collected in New South Wales (M. Cloonan, pers. comm.). Evidence to suggest that occasional human infections might occur with Stratford virus was obtained in a seroepidemiological survey in New South Wales [83], but no such evidence was found in Queensland [56].

Edge Hill virus first isolated from *Ae. vigilax* and *Cx. annulirostris* mosquitoes trapped at Cairns in 1961 [57]. Subsequent isolations were obtained from *Cx. annulirostris*, *Ae. normanensis* and *An. amictus* in Queensland [54]; *Ae. vigilax* ([74]; M. Cloonan, pers. comm.), *Cx. annulirostris* [116] and *Coquillettidia linealis* (M. Cloonan, pers. comm.) in New South Wales; and *Ae. bancroftianus* in Western Australia (A. K. Broom, R. A. Hall and J. S. Mackenzie, unpubl. res.). The major vertebrate hosts for Edge Hill virus are probably marsupials [56]. Seroepidemiological studies in Australia [83] and Irian Jaya [85] have suggested that occasional human infections occur, and in a recent report, Edge Hill virus was suggested as the possible aetiological agent in a patient presenting with arthralgia, myalgia and fatigue [2].

Sepik virus, an ungrouped flavivirus closely related to Wesselsbron virus, was isolated from *Mansonia septempunctata*, *Ficalbia flavens* and *Ficalbia spp.*, and *Armigeres spp.* trapped in the Sepik District of PNG [86, 156]. High neutralising antibody titres in the convalescent serum of a New Guinea patient hospitalised with a febrile disease makes it a suspected human pathogen [156].

Alphaviruses

Ross River virus

Ross River (RR) virus is the aetiological agent of a disease known as epidemic polyarthritis; the disease was first described during unusual epidemics at Narrandera and Hay, towns on the Murrumbidgee River in New South Wales, in 1928 [64, 128]. Subsequent outbreaks of disease with similar symptoms occurred amongst troops stationed in the Northern Territory [78] and Queensland [63, 143] during World War II. The first indication that the causative agent of these outbreaks might be a Group A arbovirus came from serological studies on patients from a major epidemic in the Murray Valley area of south-eastern Australia when another Group A virus, Bebaru, was used as antigen [144]. Shortly afterwards, the virus was isolated by Doherty et al. [61] from *Ae. vigilax* mosquitoes trapped in 1959 at the Ross River near Townsville in Queensland, after which the virus was named. However, it was not until the single largest reported outbreak in the South Pacific islands in 1979–80 that the virus was isolated from the serum of a patient suffering from epidemic polyarthritis [1]. RR virus and epidemic polyarthritis have been reviewed in detail by Marshall and Miles [114] and Kay and Aaskov [87].

RR virus has been reported from all Australian States, including Tasmania [118], as well as from the Solomon Islands [148] and PNG [85, 142, 148]. In Australia, several hundred to several thousand cases are reported annually to the Communicable Diseases Section of the Commonwealth Department of Health, Housing and Community Services [80]. Consequently, the virus is regarded as the most common cause of arboviral disease in humans in Australia. In northern and central Queensland, particularly in coastal regions, the virus is active throughout the year, while elsewhere in Australia, virus activity tends to be epidemic, following summer rains in eastern Australia, or rain and/or tidal inundation of saltmarsh in Western Australia and the Northern Territory. However, sporadic cases may occur in all months in coastal regions. Major epidemics have been reported from the Murray Valley [7], Queensland [52], central and coastal regions of New South Wales [74, 82], South Australia [124], Victoria [29], the Northern Territory [119, 147], south-western Australia [99, 101, 102], and the Pilbara and Kimberley regions in Western Australia [100].

The major clinical features of epidemic polyarthritis include various combinations of arthralgia and arthritis, usually involving joints of the extremities, myalgia, lethargy, a maculopapular rash, headache and fever [44, 70, 82, 87]. Clinically apparent infections are rare in children, the highest incidence being in the 30–40 age group [44, 82, 99, 122, 123]. In most studies, the ratio of female to male cases is equal [44, 82]. The incubation period varies between 3 days and 21 days [122, 136] with an average of 7 to 9 days [73]. Duration and severity of the polyarthritis symptoms vary substantially [44, 82]. Until recently it was accepted that severe pain, particularly in the joints of the hands and feet and in the knees may last for two to six weeks and that most patients have fully recovered after 30 to 40 weeks [87]. However, a recent follow-up study of 252 epidemic polyarthritis patients in the south-west of Western Australia found that only 2% were completely well within one month of onset of symptoms, 14% by three months and 26% by six months. Nearly half the patients were still suffering from combinations of joint pain, stiffness and swelling, tiredness and myalgia, more than one year after the onset of symptoms [44 b].

Two saltmarsh breeding mosquito species are probably the major vectors in coastal

regions, *Ae. vigilax* in northern and eastern Australia [87, 97] and *Ae. camptorhynchus* in cooler areas of southern and south-western Australia [28, 101, 102]. Minimum field infection rates as high as 1: 43 have been recorded for *Ae. vigilax* during acute epidemic polyarthritis outbreaks in the Pilbara region of Western Australia [97]. Similarly, infection rates as high as 1 : 30 have been recorded in *Ae. camptorhynchus* just prior to and during outbreaks in coastal south-western Australia (M. D. Lindsay, C. Johansen and J. S. Mackenzie, unpubl. res.). Several freshwater breeding species are also believed to be vectors of RR virus, particularly *Cx. annulirostris* [88], but also *Cq. linealis* [88, 99] and *Ae. normanensis* [25, 54, 88, 151]. Temporary freshwater ground pool-breeding species in the subgenus *Ochlerotatus*, in particular *Ae. sagax* and *Aedes* E. N. Mark's species #85[1] were implicated as major vectors during acute outbreaks of epidemic polyarthritis after heavy rains in arid inland regions of Western Australia [97, 100]. Other than the species mentioned, RR virus has been isolated from *Ae. alternans* [97, 140], *Ae. bancroftianus* [112, 138], *Ae. clelandi* (M. D. Lindsay, C. Johansen and J. S. Mackenzie, unpubl. obs.), *Ae. daliensis* [97], *Ae. flavifrons* [118], *Ae. funereus* (R. Russell, unpubl. obs.), *Ae. notoscriptus* [151], *Ae. phaecasiatus* [152], *Ae. polynesiensis* [136], *Ae. procax* (M. Cloonan, unpubl. obs.), *Ae. ratcliffei* (M. D. Lindsay, C. Johansen and J. S. Mackenzie, unpubl. obs.), *Ae. theobaldi* [112, 114], *Ae. tremulus* [97], *An. amictus* [54, 114], *An. annulipes* [112, 138], *Cx. australicus* [97, 112, 138], *Cx. quinquefasciatus* [97], *Cx. sitiens* [97] and *Mansonia uniformis* [155]. The vector competence of most of these species for RR virus and their role in transmission cycles is still to be determined.

Macropods (kangaroos, wallabies, euros) are believed to be the major vertebrate hosts of RR virus, but serological surveys have demonstrated infection in a wide range of wild, domestic and livestock animals [58, 87, 114]. RR virus may infect horses [9, 130] which may act as amplifier hosts in semi-urban areas (M. D. Lindsay and J. S. Mackenzie, unpubl. obs.). In an epidemic situation humans may also act as amplifying hosts. Man-mosquito-man transmission cycles were almost certainly the main route of virus transmission during the explosive South Pacific islands outbreaks [114]. Circumstantial evidence suggests that humans played a role in RR virus transmission cycles in the Perth Metropolitan area during an outbreak in the south-west of Western Australia in 1991–92 [99]. Serological surveys indicate that birds are less commonly infected than mammals, and apart from day-old chicks, viraemia has not been induced experimentally in any avian species [114].

Although most reports of RR virus epidemics make reference to environmental factors associated with the genesis of the epidemics, few studies have explored these factors in detail. More extensive descriptions followed investigations of the environmental parameters associated with RR virus epidemics in the south-west of Western Australia during the late springs and summers of 1988–89 [99, 101, 102]. The first outbreak was clearly associated with increased tidal heights which caused frequent and prolonged inundation of saltmarshes throughout the warmest months of the year. They were the result of higher mean sea levels which had been generated by a strengthening of the Leeuwin Current flowing down the west coast of Australia and exacerbated by continuous south-westerly weather patterns. Thus the major vector was the saltmarsh breeding *Ae. camptorhynchus* [101]. The second outbreak was associated with heavy rains and localised flooding. The

[1] This mosquito is one of many recognised as separate species by Dr. E. N. Marks, the leading Culicid taxonomist in Australia, but is as yet undescribed due to inadequate study of immature stages of the arthropod.

epidemic was initiated by exceptionally heavy late spring rains on saltmarsh habitats, generating large numbers of *Ae. camtorhynchus*. Heavy unseasonal summer rains, again resulting in areas of flooding, then served to maintain and intensify the epidemic, initially through *Ae. camptorhynchus*, then through fresh-water breeding species, including *Cq. linealis* and *Cx. annulirostris* [97, 102].

The means by which RR virus persists throughout much of Australia during droughts or winter is still not clear. In regions with tropical or temperate climates continuous, low level maintenance cycles may occur, particularly as the virus has a short extrinsic incubation period in several of its vectors and many vertebrate hosts [87]. Indeed, isolates have been obtained from *Ae. camptorhynchus* mosquitoes trapped in mid-winter in the south-west of Western Australia (M. D. Lindsay, C. A. Johansen, unpubl. res.). In many arid regions where such continuous transmission is not possible, epidemics are often characterised by the appearance of cases within two or three weeks of heavy rains [97, 100]. In the absence of evidence to implicate viraemic migratory birds as 'seeds' of such outbreaks, vertical transmission of the virus and its survival in desiccation-resistant mosquito eggs seems the most likely explanation for the sudden reappearance of virus after rains. Recently, RR virus was isolated from field-caught male *Ae. vigilax* and *Ae. tremulus* just prior to small outbreaks of epidemic polyarthritis in the arid Pilbara region of Western Australia [97]. Both species have desiccation-resistant eggs, and in their respective habitats are well suited to enable RR virus to survive periods of drought.

Isolates of RR virus from northern Queensland could be differentiated from isolates from coastal New South Wales on biological [74] and antigenic [157] grounds, suggesting that at least two phenotypic variants of RR virus are enzootic in their respective regions. Genomic relationships between 14 field isolates collected from different localities in eastern Australia and various South Pacific islands were investigated by restriction enzyme analysis using Hae III and Taq I restriction enzymes [66]. They fell into three genetic types on the basis of differences between their restriction profiles, with 1.5–5.0% nucleotide sequence divergence between the three types. No association between geographic region, vector or host of origin could be established. In a subsequent study of three human isolates obtained over a 10-month period from the South Pacific islands outbreak, considerable genetic stability was observed in nucleotide sequence from the E2 gene and the 3'-untranslated region of the three isolates, indicating a low rate of evolution [27]. The E2 gene sequence of one of the South Pacific islands isolates was compared to the sequence of the 1959 prototype strain (T48), and a divergence of 3% was observed [27]. The complete nucleotide sequences of the 1959 RR virus prototype and of a 1969 isolate from New South Wales have been obtained and, excluding deletions and insertions, the two isolates exhibited a sequence divergence of 2.4% [67].

In an extensive study of RR virus genomic relationships, 80 isolates from around Australia and South Pacific islands were recently compared by RNase T1 resistant oligonucleotide fingerprinting. Four groups (called topotypes) with distinct patterns of the large oligonucleotides were found, but the patterns could not be aligned. Divergence between the topotypes was assumed to be > 5–6%. Two topotypes were represented by a single isolate, the other two, characterised by isolates WK20 and T48, comprised 27 and 51 members, respectively [98].

The T48 topotype contained three major clusters of isolates. The largest contained isolates from all regions represented in the study, indicating a wide geographic distribution

of this genotype. This is inconsistent with the limited dispersal or movement of the regular vertebrate hosts (macropods and other marsupials). Presumably, this genotype was transported in viraemic vertebrates (humans or livestock) travelling by air. A second cluster in the T48 topotype consisted of three isolates from one geographical region (Charleville, Queensland) obtained over a 5-month period in 1976. The third cluster contained early isolates (1968–70) from Nelson Bay in NSW and single isolates from Queensland and the Northern Territory. The Queensland isolate was linked at a lower level than the other members. Recent isolates from Nelson Bay were quite different from the early ones and were grouped in the first cluster, suggesting that the early genotype may have disappeared or been replaced.

The other major group (WK20 topotype) contained two clusters. Each of these contained isolates from the south-west of Western Australia, the Kimberley region, and the Northern Territory. This suggests the circulation of two distinct genotypes within this large region. In addition, the single members of the remaining two topotypes, each of which is substantially different from all other isolates, also come from this region. Viruses belonging to the WK20 topotype had been isolated between 1977 to 1990. No viruses isolated after 1989 in the south-west of Western Australia belong to one of the two clusters, suggesting that this genotype disappeared after 1989. Isolates belonging to both clusters were isolated from pools of *Ae. camptorhynchus* caught in the same trap, which suggests the existence of co-circulating strains.

In this study, no evidence of an association between clusters and hosts of origin was found; it is interesting to note, however, that a human isolate obtained during an epidemic in the south-west of Western Australia was homologous to an interepidemic mosquito isolate from the same region. This suggests that epidemics are vector- and host-driven and depend upon environmental conditions which lead to increased levels of virus transmission rather than on the introduction or evolution of new virus strains.

Preliminary studies have shown that virus strains representative of each topotype differ in neutralisation assays with polyclonal antisera and display substantially different ELISA patterns with panels of monoclonal antibodies raised against each of the topotypes (N. M. Oliveira, R. A. Hall, M. D. Lindsay, A. K. Broom, J. S. Mackenzie and B. H. Kay, unpubl. res.).

Barmah Forest virus

BF was first isolated from *Cx. annulirostris* mosquitoes collected in 1974 in northern Victoria [116] and characterised as an alphavirus, despite cross-reactions with Umbre virus, a bunyavirus [45]. Human infection causing an epidemic polyarthritis-like disease was first reported in 1986 [149], and the virus was successfully cultivated from a patient in 1988 [134]. Sporadic cases of BF infection have been reported from New South Wales [12, 81], Queensland [40, 131, 133, 134], and Western Australia ([41]; D. W. Smith, unpubl. obs.).

The first major serologically confirmed outbreak occurred in 1992 in the Northern Territory [119]. Between December 1991 and April 1992, 187 cases of an alphavirus-like illness occurred at Nhulunbuy in the north-east of the Northern Territory. The major symptoms were joint pains, rash, tiredness and fever occurring in non-Aboriginal residents of the area. Serological tests demonstrated 36 cases of BF virus infection, 23 cases of RR virus infection, and 7 with evidence of dual infections. Analysis of the cases with definite

single BF virus or RR virus infections showed a similar symptomatology. However, BF virus caused significantly more rash than RR virus (98% vs. 70%) while arthralgia and arthritis were less common than with RR virus (86% and 30% versus 98% and 61%, respectively). Symptoms persisting for at least 6 months were seen in some cases of both RR and BF virus infection. Antibody responses to BF virus (as measured by haemagglutination inhibition and indirect immunofluorescence for IgM) were detected later than in RR virus infections. IgM responses to both viruses were detectable for at least 6 months after onset of illness (A. Merianos and D. Smith, unpubl. obs.).

Little is known of the vector species and vertebrate hosts of BF virus. Isolations have been made from *Cx. annulirostris* in New South Wales [116], Queensland [54], Northern Territory [146, 151] and Western Australia (M. D. Lindsay, C. A. Johansen, A. Wright and J. S. Mackenzie, unpubl. obs.) which may therefore be the most widespread vector species. Isolations have also been reported from *Ae. vigilax* in New South Wales [149], Queensland [54], Northern Territory [152] and Western Australia (M. D. Lindsay, C. Johansen, A. Wright and J. S. Mackenzie, unpubl. obs.); from *Ae. normanensis* in Queensland [54] and Northern Territory [152]; from *Ae. bancroftianus* in Western Australia [23] and New South Wales (I. D. Marshall, pers. comm.); from *Ae. camptorhynchus* in Victoria [4] and Western Australia (M. D. Lindsay, C. A. Johansen and J. S. Mackenzie, unpubl. obs.); from *Ae. eidsvoldensis*, *Ae. pseudonormanensis*, *An. annulipes* and *An. amictus* in Western Australia [23]; from *Cq. linealis* in Western Australia (M. D. Lindsay, C. A. Johansen and J. S. Mackenzie) and from *Culicoides marksi* in the Northern Territory [146]. The latter is the only report of an isolation of an alphavirus from an arthropod other than mosquitoes in the Australasian zoogeographical region.

There has been no evidence of BF virus activity in PNG.

Sindbis virus

SIN virus is widely distributed throughout Australia, except Tasmania, with isolations particularly from *Cx. annulirostris* and *Ae. normanensis* mosquitoes (e.g. [23, 24, 54, 57, 96, 152]). Indeed SIN is the most commonly isolated arbovirus from mosquitoes in Australia, while only a single isolate has been reported from PNG [156]. Birds are the major vertebrate hosts. Human disease due to SIN is characterised by fever with a vesicular rash; seroepidemiological studies suggest that occasional subclinical human infections occur in Australia [14, 48, 85, 95] and PNG [85, 148], but disease has only been reported on two occasions [53, 75]. This contrasts with the situation in parts of Africa, northern Europe and Russia where outbreaks involving several hundred cases due to SIN- or SIN-related viruses have been reported (reviewed in [127]). Strain variation [129] or the presence of clinically similar diseases or antigenically related alphaviruses may explain this phenomenon.

A genetic analysis of 19 SIN isolates from different regions of Australia was carried out using the ultrathin layer RNase T1 oligonucleotide mapping technique. All isolates were grouped in clusters that were linked at a similarity coefficient of > 78% (T. N. H. Brand, R. J. Coelen and J. S. Mackenzie, unpubl. obs.). This similarity indicated a genomic divergence of only about 1.5%. Therefore, a single major genetic type of SIN appears to be distributed over the entire Australian continent. A small degree of clustering separated the isolates from Queensland and New South Wales from the remaining isolates. However, the distribution of one topotype across the entire Australian continent is a feature shared with other Australian arboviruses which have migratory birds as their principal vertebrate host [30, 68].

Other alphaviruses

Other alphaviruses have been isolated in the Australasian zoogeographic region, including Getah virus in Australia and Whataroa virus in New Zealand. They have not been associated with human disease although Getah antibodies have been found in sera in Australia and PNG [49, 85]. Chikungunya virus has not been reported in the Australasian zoogeographic region.

Bunyaviruses

Seroepidemiological surveys have demonstrated antibodies to Gan Gan and Trubanaman bunyaviruses in human sera collected in Australia [13, 62, 149]. Gan Gan virus was first isolated in 1969 in New South Wales from *Ae. vigilax* [74], then from *Ae. vigilax* [115], *Cx. annulirostris*, *Ae. eidsvoldensis*, *Ae. normanensis* and *Ae. theobaldi* [50, 54]. Trubanaman virus was first isolated in Queensland in 1965 from *An. annulipes* [60], and later from *An. annulipes* in the Murray Valley area of south-east Australia [111], New South Wales (M. Cloonan and R. Russell, pers. comm.), the south-west of Western Australia (M. D. Lindsay, C. A. Johansen and J. S. Mackenzie, unpubl. res.), and from *Cx. annulirostris* in the north of Western Australia [94] and in New South Wales [155].

No disease has been associated with Trubanaman virus, but Gan Gan virus has been implicated with an acute epidemic polyarthritic-like illness in 3 patients [13].

General comments

The involvement of certain Australian arboviruses in human disease is now well established, but often the extent of their involvement is less well understood. Most arboviruses cause subclinical rather than clinical infections, and many arboviral diseases are probably not diagnosed because they cause such non-specific symptoms as rash, fever and malaise [51]. The pathogenic role of the lesser known Australian flaviviruses such as Alfuy, Stratford, Edge Hill and Kokobera viruses is not clear. They have only occasionally been associated with human disease, but recent serological studies in New South Wales have shown that antibodies are present in a large percentage of the population [83]. Although all human arboviruses can cause subclinical and non-specific symptoms, all major arboviral syndromes occur in Australia: encephalitis, polyarthritis with or without a rash, and rarely haemorrhagic fever. There are also as yet unrecognised arboviruses that can cause human disease. During an outbreak of RR virus in 1988–89 over 200 cases of a disease with symptoms similar to those caused by RR virus were reported in the south-west of Western Australia (M. R. Bucens, pers. comm.). Sera from these patients were tested against most known Australian arboviruses but no likely causative agent was identified. Similar outbreaks of an unknown arbovirus-like illness have been reported from the Northern Territory (B. Currie, pers. comm.). In addition, a seroepidemiological survey in New South Wales has strongly indicated the presence of unknown flaviviruses causing human infections [84].

There is growing concern internationally about the emergence and resurgence of infectious diseases and the increasing threat for human and animal health. Arboviral diseases are especially hazardous due to a number of factors including changes in land use and deforestation providing new habitats for mosquito breeding, and increased interactions between vectors and vertebrate hosts; the lack of potent, environmentally safe insecticides for vector control; and increasing international travel and transportation allowing rapid

spread of vectors and viruses. Exotic arboviruses may be introduced by these means into countries of the Australasian zoogeographic region. Potential vectors hosts for e.g. Japanese encephalitis virus, West Nile virus and Chikungunya virus probably exist in Australia and PNG, and for this reason there has always been concern that they may become established upon importation. The ability of certain arboviruses to take advantage of rapid air travel between countries was well demonstrated by the export of RR virus from mainland Australia to the South Pacific in 1979–80, probably through a viraemic traveller, and by the rapid spread of dengue in tropical areas of the world. Indeed, dengue has probably been periodically reintroduced into Queensland to initiate the epidemics discussed above, and every year cases of exotic arboviral infections such as Japanese encephalitis and Chikungunya are diagnosed in travellers arriving in Australia. The possible introduction of exotic mosquito species into Australia or New Zealand, particularly of *Ae. albopictus* and *Ae. aegypti* (into Western Australia, the Northern Territory and New Zealand), is also of considerable concern. Thus active monitoring and surveillance is essential.

Finally, climatic changes associated with the Greenhouse Effect may increase the incidence of arboviral disease in Australia [102, 109], both for endemic and exotic arboviruses. Knowledge of the ecology and incidence of Australian arboviruses, of their role in human disease and of potential vectors and their competence to transmit will be essential for our understanding of the potential risks to human health and for developing strategies to minimize these risks.

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