

Rheumatoid arthritis

Another viral candidate

from K.A. Brown

DEVOTEES of the school that believes an occult virus is responsible for the induction of rheumatoid arthritis will have welcomed a recent article summarizing a three-year collaborative study undertaken in three USA centres on the identification of parvovirus-like particles in synovial tissue from the joints of rheumatoid arthritis patients¹. For the sceptics in this field, the publication heralds the arrival of yet another viral candidate whose association with rheumatoid arthritis, if any, will be shown to be circumstantial and which warrants investigation simply because it is one of the few viruses which has not already been the subject of an attempt to associate it with the disease.

The research of Simpson *et al.* stems from their isolation of an infectious agent, termed RA-1, from rheumatoid synovial cells, co-cultured with human lung fibroblasts or rabbit fetal synovial cells, and subsequently passaged in suckling mice. Injection of RA-1 into the cerebral area of the brain of neonatal Swiss-Webster mice produced a fatal neurological disease, whilst its inoculation into the peritoneum produced several symptoms, notably permanent crippling, alopecia, conjunctivitis and dwarfism. Such fatalities and disabling effects were not induced by synovial extracts prepared from patients with the non-inflammatory disorder osteoarthritis.

In their size (24–25 nm), morphology and resistance to chemical and physical treatment, the infectious particles resemble a parvovirus. Parvoviruses are among the smallest of the DNA viruses. There are two main genera: the adeno-associated, whose replication is 'defective' and requires the help of a co-infected adenovirus; and the adeno-independent, whose replication does not require assistance. In domestic animals parvoviruses are believed to be responsible for such conditions as panleukopenia and enteritis in cats and hepatitis in dogs and geese. Human 'serum parvovirus-like virus' was discovered during the screening of symptom-free blood donors for hepatitis B virus antigen². This adeno-independent virus, often referred to as the B19 virus, was shown to induce febrile illnesses in haematologically normal people³, aplastic crisis in patients with haemolytic anaemia due to infection of a haematopoietic progenitor cell⁴ and to be transmitted to haemophiliacs in blood clotting factor concentrates⁵.

Since established laboratory cell lines may be contaminated with parvovirus, there is always a risk of parvovirus contamination during the co-culture and passage stages of experiments. However, Simpson *et al.* show that injection of

rheumatoid arthritis synovial cells into murine brains, without prior co-cultivation with accessory cells, induces the appearance of the RA-1 virus. Furthermore, the RA-1 antigen does not react with antisera directed against several other parvoviruses which infect mice and other animals.

On caesium chloride equilibrium gradients, the RA-1 viral particles are found at a density of 1.30–1.43 g cm⁻¹. In a collaborative study which is shortly to be submitted for publication, Gabi Stierle, a visiting scientist to our department, demonstrates that caesium chloride fractions of 1.41 g cm⁻¹, prepared from synovial cells of five of eleven rheumatoid arthritis patients, but none of six osteoarthritis patients, react with an antibody against RA-1. The immunoreactive rheumatoid fractions contain abundant particles of 10 nm diameter whilst 23 nm particles are seen in similar isolates from long-term rheumatoid synovial cultures. The rheumatoid fractions do not react with the monoclonal antibodies to the B19 virus. This finding, together with the failure of the B19 virus to react with the anti-RA-1 antibody and the high prevalence of the anti-B19 antibody in 61 per cent of the population⁶, suggests that it is unlikely that the B19 virus has an important role in rheumatoid arthritis¹.

Parvovirus is the infectious agent of Aleutian disease in mink, a slowly progressive fatal disorder characterized by hypergammaglobulinaemia, anaemia, immune complex-mediated arteritis and

glomerulonephritis⁷ and thought by some investigators to have features of autoimmune disease. There is no evidence to suggest that parvovirus may directly initiate a synovitis, though the affinity of the virus for host cells that are of high mitotic activity, particularly activated lymphocytes⁸ and endothelial cells⁹, and its dissemination by monocytes and macrophages⁸ are attributes which might be expected of a polyarthritogenic agent. It is premature to indulge in conjecturing possible implications of the work of Simpson and Stierle for rheumatoid arthritis. We must await definitive characterization of the RA-1 virus by techniques such as cell hybridization, serological evidence of parvovirus infection, laboratory studies performed on patients with inflammatory arthritides other than rheumatoid arthritis, and cytopathogenic studies using adenovirus and other viruses which might support its replication.

Simpson *et al.* are to be encouraged in their persistent and patient search for a replicating virus in rheumatoid arthritis, a task that seems fraught with almost insurmountable biological and technical obstacles. Whatever the outcome, they will have resurrected interest in an area which urgently requires more motivated scientists of enthusiastic application and original approach. Progress is painfully overdue. □

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100 years ago

PILE-DWELLINGS ON HILLTOPS

AMONG the Miris, Singphus, Kamtis, Nogas, Mismis, and Deodhains that I have questioned as to the origin of the custom of building on piles, the answer is invariably that they do not know, that it is their tribal custom, &c. Pressed as to the advantages of it, or why they could not build on the ground like Hindus, they generally end by urging the absolute necessity of keeping things out of reach of the ever-present pig.

As an illustration of how this animal practically affects the question of house-building, I append a section of a typical average Noga house, as built by the tribes south-east of Sibsagar to the Upper Dihing. One end generally rests on the ground, while the other overhangs a slope for which there often seems to be no

occasion, as plenty of level land is about. In all houses of this type the end devoted to husking rice rests on the ground, and the door at the end has a slab that can be raised to admit pigs to eat the husks. This compartment (one-third of the house) is divided from the living and sleeping part by a wall and a door with a stile to keep out pigs. There are generally from two to six, or more, sleeping-rooms on the ground, and beyond them again is an open room used for visitors, or to sit and work in during wet weather.

But there are many other things besides pile-dwellings that prove these now distinct tribes to have descended from a common stock. The "morongs," or houses in which the lads and single men sleep at night, away from their parents' houses, are seen under various names all through these hills. There are also "morongs" for the girls and single young women, and there are special and peculiar laws relating to morongs. Liberty of the sexes before marriage is indeed practically so complete among all these tribes that really *morals begin with marriage*. After marriage they are better, I think, than civilised nations.

