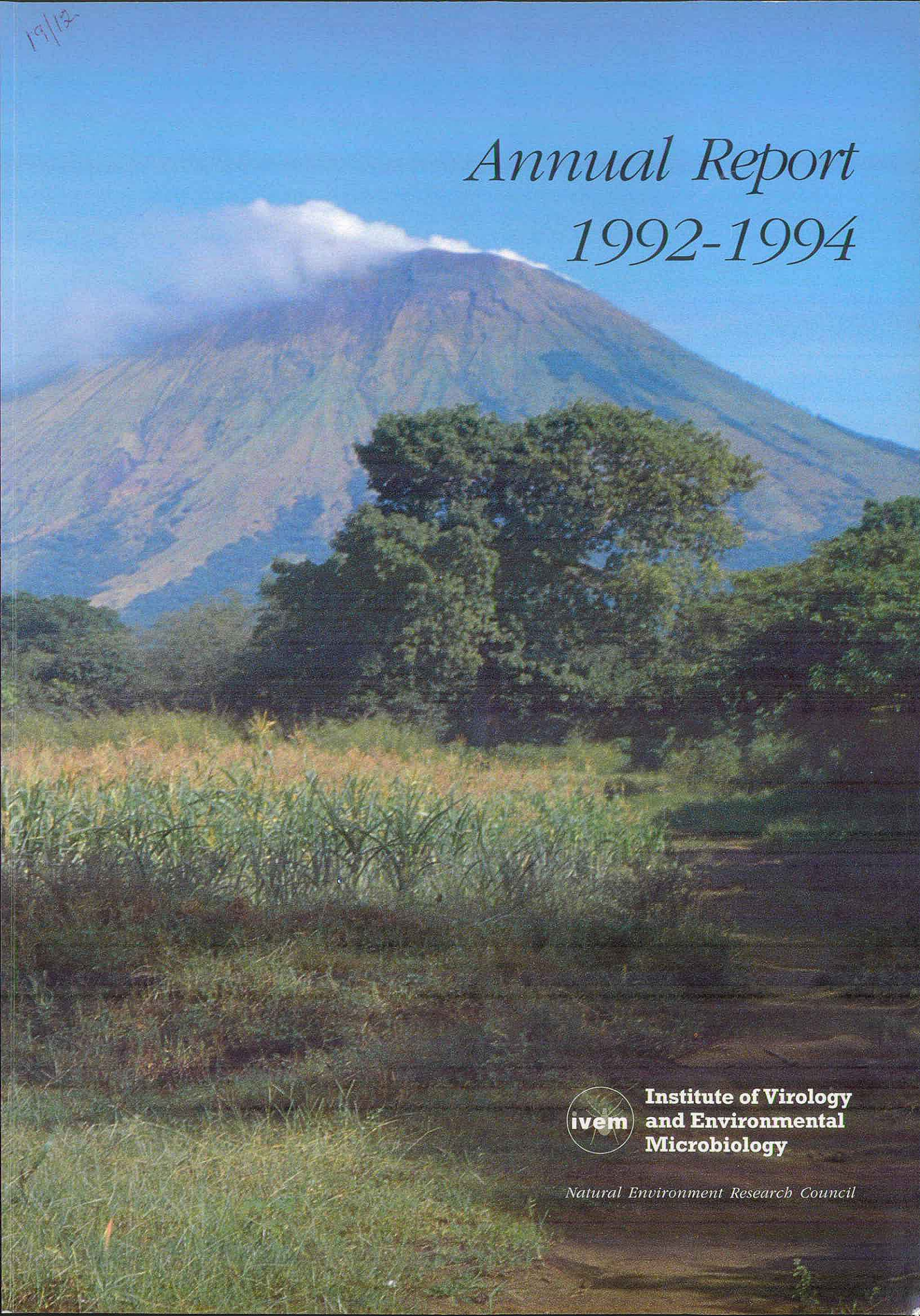

Annual Report 1992-1994

Institute of Virology and Environmental Microbiology

Natural Environment Research Council

Foreword

The past year has been one of considerable change in NERC, both in the focus of its science and in its structures. The catalyst for these changes was the publication of the White Paper *Realising our Potential.* NERC was given a new mission for its science to embrace the concepts of meeting the needs of its user communities and contributing to wealth creation and the quality of life. We have, of course, always paid close attention to these objectives, but there is now a clear need for a sharper focus and better articulation of what we do in these areas. Basic science and long-term monitoring are also included in our mission, and due weight must also be given to these when developing our science strategies.

The science directorates will cease to exist towards the end of 1994, and new structures will be put in place. TFSD Institutes are being regrouped as the Centre for Ecology and Hydrology. However, the report of the Multi-Departmental Scrutiny of Public Sector Research Establishments is awaited, and decisions arising from this may result in further organisational changes within NERC.

An important activity during the year has been the preparation of a new science and technology strategy for the terrestrial and freshwater sciences. Publication is expected in July, and a number of research areas will be identified for priority support over the next five years.

During my relatively short time with NERC, I have come to appreciate and value the breadth and strength of our work in the terrestrial, freshwater and hydrological sciences. This Report illustrates the wide range of projects on virology and environmental microbiology that are undertaken at IVEM. I find it particularly impressive that, across the whole spectrum of the Institute's activities, basic research of the highest quality is leading to potential applications of the science in areas as diverse as plant protection, vaccine production and gene delivery systems.

Finally, I should like to state how much I have appreciated the friendships that I have established with so many members of our community. It is these that will be my most valued and lasting memories of NERC.

C Arme
Director of Terrestrial and Freshwater Sciences

Front Cover Illustration:
Maize crop treated with insecticides to protect against ***Spodoptera*** *caterpillar pests in Nicaragua.*

NATURAL ENVIRONMENT RESEARCH COUNCIL

REPORT OF THE INSTITUTE OF VIROLOGY AND ENVIRONMENTAL MICROBIOLOGY 1992-1994

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Director's Statement

The Institute of Virology and Environmental Microbiology is a component of the Natural Environment Research Council (NERC), an organisation funded by an annual grant from the UK government to support and undertake research in the sciences relating to man's environment.

The mission of the Institute is the study of viruses and other microbes in the natural environment primarily in the following areas: their relationships with vertebrates, invertebrates and plants; their replication, transmission, vectors, hosts, and ecology; the generation and behaviour of genetically modified organisms, the risks and benefits of their release, together with appropriate aspects of the molecular biology, evolution and genetics of microbes; and the identification, prevention and spread of diseases caused by microbes, primarily in species other than man. The Institute carries out strategic and basic research in these subjects, and also provides expertise for sponsored research and training of high quality. It aims to build its sponsored research on the foundation of a first class scientific reputation and to play a major part in the national and international scientific community.

Prior to 1980 the staff were members of Oxford University and known as the Insect Pathology Unit (1963-1971), then the Unit of Invertebrate Virology (1971-1980) when support was provided by NERC. In 1980 the Institute of Virology was founded. Prior to 1984 the research was under the direction of Dr T W Tinsley MA, DSc, FI Biol, in conjunction with Mr J S Robertson BA. Since 1984 the Director has been Professor D H L Bishop MA, DSc, F Biol. In 1989 the name and remit of the Institute was expanded to the Institute of Virology and Environmental Microbiology (IVEM) as the expertise of the staff increased to include research into other aspects of environmental microbiology.

The Institute of Virology and Environmental Microbiology is housed in a custom-built facility on a site allocated to NERC pro temporis by the University of Oxford. The Institute is in the heart of the University's Science Area. The arrangement allows direct links to be maintained between the staff of the Institute and those of several Departments of the University. Almost all the project leaders of the Institute, together with their Oxford University or Oxford Brookes University partners, undertake the supervision of graduate students. Staff of the Institute maintain close links with the Oxford University Interdisciplinary Research Centre (IRC) in Molecular Sciences.

This report, a synopsis of the research areas and a selection of the achievements in the ten programmes of the Institute, covers research performed over the last 2 years (1992-1994). Signal achievements include, among others, the completion of the 133,984 base pair genome sequence of a baculovirus insecticide, field trials of a genetically improved version of this virus, and morphogenetic studies of how orbiviruses assemble at the molecular level. Details of the results will be found in the publication record.

David H L Bishop

Microbial Ecology

M J Bailey

We are investigating the properties of selected pseudomonad bacteria and their interactions with sugar beet. To achieve this we have developed and tested in laboratory, greenhouse and field studies, a genetically marked bacterial species in order to follow the ability of this species to colonise plant surfaces and interact with other members of the natural microbial community. The studies have as their eventual objective the use of genetically modified bacteria to control against pest infestations and plant pathogens. In addition, studies have been undertaken to establish the genetic properties of a plant-associated pseudomonad as an aid to understanding its taxonomic relationships. Selected aspects of the work are described below.

Studies on the microbiology of plant surfaces using a genetically marked species

Using a common and naturally occurring plant-associated bacterium and genetic engineering procedures, a plasmid-free, doubly-marked *Pseudomonas aureofaciens* species, designated SBW25EeZY6KX (lacZY, kan^r, xylE), was developed. Following laboratory and greenhouse studies, and with permission from the Secretary of State for the Environment, the marked bacterium was used to investigate the ability of the species to colonise, compete and persist on sugar beet surfaces throughout two growing seasons (Figure 1). Similar field studies were undertaken with the bacterium by collaborators at the Horticulture Research International (Littlehampton) using wheat as the plant substrate. The markers, set some 15% apart on the bacterial chromosome, allowed the bacterium to be monitored, identified and quantified among the microbial population using simple plating methods. These procedures also allowed the bacterium to be detected at levels down to 1 colony forming unit (cfu) per gram of soil sample. Introduced as a seed dressing to sugar beet (10^7 cfu per seed), the bacterium effectively colonised the roots and leaves of developing plants in competition with other species (bacteria, fungi), but did not survive in detectable numbers in the soil in the absence of plant material. Over Winter it survived, and in the second year colonised new leaves that grew on the previously inoculated plants. No dispersal of viable bacteria to soil, weeds or neighbouring plants was detected, except to those that were in direct contact with the heavily colonised plants, and then only in very small numbers. The studies were undertaken with support from **the Department of the Environment**.

***Figure 1**: Sugar beet field site*

Do chromosomally located genes transfer to indigenous bacteria in the phytosphere?

To detect gene transfer in the environment it was assumed that the most likely natural recipients of chromosomally-located genes would be other pseudomonads. During the studies described above, the presence of the marker genes was sought among other fluorescent pseudomonads isolated from the sugar beet. No gene transfer was detected despite the sensitivity of the assays.

A genetic map of a natural pseudomonad

A complete physical map of the 6,600,000 base-pair genome of the *P. aureofaciens* SBW25 chromosome has been obtained using restriction enzyme digests, one and

two-dimensional pulse field gel electrophoresis, as well as available pseudomonad gene probes and cosmid subclones of the bacterial genome. The locations of 120 restriction sites (15 *Pac*I, 52 *Spe*I, 53 *Xba*I) have been placed on the genetic map together with a number of genes including *ori*C, *rec*A, *opr*F, pyoverdin and the various rRNA operons. This is the first map of an indigenous plant-associated pseudomonad to be described and provides a reference for understanding the bacterial genome organisation and pseudomonad genetics.

Conjugative plasmid transfer is stimulated in the rhizosphere

Six genetically distinct classes of natural conjugative plasmids that provide host bacterial species with resistance to mercury were isolated from the phytosphere community of sugar beet over a number of growing seasons. *In situ* investigations with one of these plasmids demonstrated that transfer between introduced donors and recipients was stimulated at the root surface, but was not detected in soil free of root exudates. *In situ* transfer on the plant surfaces was more than 100 times greater than that observed using agar as a substrate (Lilley *et al.*, 1994, Microbiology **140**: 27).

Transfer of indigenous mercury resistance plasmids to a genetically marked pseudomonad associated with field grown sugar beet

With support from **the Ministry of Agriculture, Fisheries and Food, the European Community** and **the Department of the Environment** we have investigated whether the transfer of mercury resistance plasmids occurs in the natural environment under field conditions. The acquisition of such plasmids was monitored among the marked bacteria recovered from field grown sugar beet. Mercury resistant colonies of pseudomonads containing the two marker genes were recovered from the leaves and roots of mature plants. Unlike the parent bacterium, these bacteria were shown to contain plasmids with DNA sizes ranging up to 300,000 base-pairs in size and representing two genetically distinct groups. The results provide the first unequivocal demonstration of conjugative gene transfer in the phytosphere under natural conditions.

Molecular Virology

D H L Bishop

The research undertaken by the Molecular Virology group concerns defining the genetic capabilities, coding and morphogenetic strategies of selected viruses and the consequences of virus infection. To accomplish these goals, use is made of genetics and genetic engineering procedures to prepare reagents for analysis and to investigate the characteristics of the derived products. Including the work supported by grants and contracts, the viruses under study have been rabies, feline immunodeficiency virus, selected human caliciviruses, hepatitis A and the bunyaviruses snowshoe hare and La Crosse viruses. Selected topics are described below, for fuller accounts see the complete Bibliography.

The genetic capabilities of bunyaviruses: new evidence that polyploidy is a common feature of bunyavirus infections

Members of the Bunyaviridae family include a variety of human and animal pathogens. While most members of the family are transmitted by arthropod vectors, some, the hantaviruses, are transmitted by particular rodent species causing disease in their incidental human hosts (e.g., the 1993 "Four Corners" virus epidemic in the USA). Bunyaviruses, one of the 5 genera in the family, include some 150 virus species. They are transmitted by mosquitoes and, on occasion, by certain other haematophagous arthropods. Generally the viruses are limited in their distribution by the particular hosts and vectors they infect. Snowshoe hare (SSH) and La Crosse (LAC) bunyaviruses have been recovered from the USA and Canada in association with human infections, in particular involving children. Varieties and relatives of these viruses, including Tahyna and Lumbo viruses, are members of the same gene pool and have been found in other regions of the world (Europe, South Africa, Russia, South and Central America). Several are associated with human infections. All members of the Bunyaviridae family have a tripartite RNA genome that may reassort between members of the same gene pool upon coinfection of host cells (vertebrate or invertebrate). Apart from the accumulation of point mutations, reassortment is a major form of evolution amongst RNA viruses that have segmented genomes. In view of this, a study was conducted using polymerase chain reactions (PCR) specific for the individual L, M, and S RNAs of SSH and LAC viruses in order to investigate the factors that affect the formation of reassortants. All 8 possible genotype combinations were identified (2^3), with results that indicated a preference for homologous LM and MS associations and hence the formation of the parental genotypes. However, an unexpected observation was the high percentage (9%) of polyploid virions involving the similar RNAs of both viruses (i.e., infectious viruses that contained more than one type of a particular RNA species e.g., the S RNAs of both LAC and SSH viruses). Progeny virus species with both S types were more frequently obtained than species with both M RNA types. On the assumption that polyploidy occurs with at least equal frequency in the replication of individual bunyaviruses, this observation offers a further explanation for the difficulties reported previously in obtaining temperature sensitive mutants representing the S RNA gene products of bunyaviruses. [Other explanations are the small percentage of the S RNA target size and the overlapping reading frames of the 2 encoded genes (Bishop *et al.*, 1982, Nucleic Acids Research **10**, 3703).] The presence of polyploid viruses undoubtedly reflects the plasticity of the morphogenetic processes of these enveloped viruses. Apart from the value of possessing more than one copy of an RNA segment, co-packaging of a foreign segment has implications for virus evolution. For example, a passenger gene may have an opportunity to adapt to the host genotype without the requirement to provide functions needed for virus replication. The further question raised by these studies is whether polyploidy is a common feature among other

enveloped viruses with segmented genomes (e.g., the influenza viruses).

PCR procedures to identify human caliciviruses

With support from a contract from **the Ministry of Agriculture, Fisheries and Food**, and based on the reported sequences of a number of human caliciviruses (the Norwalk, Snow mountain, Southampton and hepatitis E viruses), PCR procedures have been established to allow the presence of such viruses to be identified in contaminated shellfish samples. Similarly, PCR procedures have been established for other potential viral contaminants, such as hepatitis A virus.

Morphogenetic studies on hepatitis A virus

With support from **The Wellcome Trust**, studies have been undertaken on the synthesis of hepatitis A virus-like particles (VLPs) using baculovirus expression vectors and with regard to developing a candidate vaccine to the virus that can be prepared in insect cells. A variety of single and dual gene baculovirus expression vectors were made involving the complete P1 coding region of hepatitis A virus expressed in the presence or absence of the various viral proteases, or involving modifications of the amino terminal sequence of P1 to provide an optimal myristoylation site. Similarly, the individual P1 encoded products were made either individually or all together. Synthesis of the various products was analysed and the expression levels optimised. To achieve the latter, selected codons were changed (e.g., GGA for GGG as a glycine codon, etc.) on the basis that such codons are infrequently employed in the baculovirus genome. While antigenic sequences were obtained and the expected protease activities were demonstrated, little evidence for VLP formation was obtained, unlike the prior studies with polio VLPs (Braütigam *et al.*, 1993, Virology, **192**, 512).

Feline immunodeficiency virus (FIV)

With support from **Laboratoires VIRBAC**, various FIV gene products have been expressed, diagnostic reagents prepared and the characteristics of the *gag-pol* ribosome frameshift event have been characterised. To test some of these reagents, the incidence of FIV-reactive antibodies in free-ranging lions in the Kruger and Etosha National Parks in Southern Africa was investigated. While no evidence for FIV-related infections was identified in Etosha, in the Kruger National Park 83% of the lion samples dating back to 1977 were found to have reactive antibodies. Apart from the lower prevalence in cubs (50%), no particular trends were demonstrated in terms of age, sex, date, or geographical origins of the samples in the Park. The engineered FIV antigen was shown to be more sensitive at detecting FIV-reactive antibodies than assays with available commercial kits.

Virus Ultrastructure

T F Booth

The research undertaken addresses the question of defining the ultrastructure of selected viruses and relating this to their morphogenesis. The system under study concerns bluetongue virus (BTV) and was instigated in collaboration with Professor Roy and her associates. To bridge the gap between X-ray crystallography at the atomic level and direct visualisation of a particle, use is made of cryo-electron microscopy. Cryo-electron microscopy involves ultra-rapid freezing of biological macromolecules in a thin layer of vitreous ice. Specimens are then transferred into a transmission electron microscope equipped with a low-temperature specimen holder. Due to the lack of artefacts with this technique, image processing of the micrographs yields an accurate three-dimensional map of the structure of macromolecular assemblies such as virus particles and at resolutions of up to 2.0 nm. The rapidity of freezing ensures that labile structures, such as lipid membranes and protein assemblies, are preserved and that the shapes and relative positions of component molecules are maintained. Another benefit is the possibility of time-resolved studies during dynamic events such as viral uncoating or maturation. With cryo-techniques valuable information from within the molecular structures can also be obtained, unlike with conventional shadowing or negative staining techniques (which only allow the surfaces of molecules to be visualised).

In collaboration with Dr E A Hewat and R H Wade in Grenoble and Professor P Roy in Oxford, we have analysed CLPs and VLPs and compared them to BTV virions and cores. The 3D structures generated by computer analysis of cryo-electron micrographs have been obtained. The VLPs are essentially similar to that of the virus particles (Figure 1), except that they are empty and contain no genomic, or cellular RNA, or replicative enzymes. However, the VLPs are slightly collapsed inwards at the five-fold vertices, and thus have a slightly different shape to that of virus particles. Analysis of apparently perfectly formed VLPs indicates that they have a full complement of the four main proteins (VP2, 3, 5 and 7), with all positions occupied to a high degree. Moreover, the VLP contains a full complement of the VP7 trimers, some of which can be missing from CLPs. This suggests that interactions with the outer shell proteins may stabilise the VP7 trimers around each five-fold axis.

The recent installation at IVEM of a Philips CM120 cryo-electron microscope, with an Oxford Instruments cryotransfer stage will facilitate further studies and should allow significant improvements in understanding virus ultrastructure. Developmental studies are supported by a collaboration with **Oxford Instruments (UK) Ltd**.

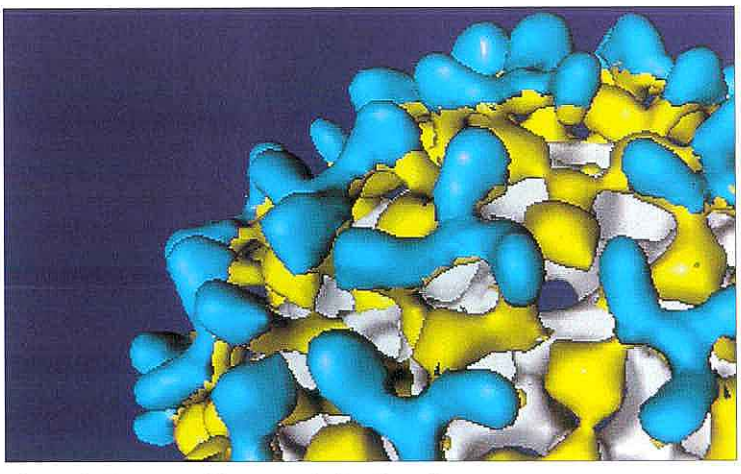


***Figure 1**: Structure of the outer shell surface of bluetongue virus consists of two types of protein subunits, 180 VP2 subunits (in blue) arranged in propeller-like clusters of three, and 120 globular VP5 subunits (yellow) which fit into sockets in-between. The inner shell layers are shown in grey. The diameter of the particle is 84nm.*

Self-assembly of BTV proteins into core-like and virus-like particles (CLPs, VLPs)

The discovery by Professor Roy and colleagues (French and Roy, 1990, J. Virol., **64**: 1530; French, Marshall and Roy, J. Virol. **64**: 5695) that when certain BTV proteins are expressed together in cells, they self-assemble into CLPs and VLPs, has allowed

their structures to be compared to those of virus cores and particles and the morphogenetic processes to be dissected. When the VP3 and VP7 proteins of BTV are expressed, icosahedral, single-shelled CLPs are formed spontaneously (see the Orbivirus Report). If the outer capsid proteins VP2 and VP5 are expressed at the same time, double-shelled VLPs are formed containing all four proteins. The surface structure of VLPs is similar to that of the virus particle, as shown in Figure 1.

Plant Virology

J I Cooper

The plant virology group undertakes research to understand the factors that determine plant resistance to viruses, and to develop methods to protect plants against virus pathogens and pest infestations. To accomplish these goals we are using a variety of genetic engineering techniques to introduce appropriate virus genes (or truncated genes) into plants and plant cells. The products are being evaluated for suitability in agriculture and forestry.

Transgenic genes protect against root inoculation by virus-carrying nematodes

Soil-inhabiting nematodes injest viruses from infected plants when they feed on the roots. Such viruses transmitted by nematodes cause disease in wild plants and lessen the competitiveness of individuals and populations in communities. In some instances, the viruses cause severe damage to food/fibre crops. Control measures to eradicate soil-inhabiting nematodes are expensive, inefficient, and often environmentally unacceptable. As a consequence, we are developing biotechnological methods of controlling plant resistance to infection by these nematode transmitted viruses.

One strategy employs the capsid protein gene of arabis mosaic virus (ArMV) or that of strawberry latent ringspot virus (SLRSV). Each of these viruses is transmitted by the nematode species *Xiphinema diversicaudatum*. Evidence has been obtained to indicate that transformed plants containing the SLRSV or ArMV capsid protein are resistant to homologous virus infection. The capsid gene of ArMV has been genetically engineered into tobacco plants. Furthermore, these transgenic plants are significantly less susceptible to systemic invasion following inoculation by nematodes carrying the homologous virus. These observations have provided the first reported evidence that expression of a capsid protein protected transgenic plants against nematode-transmitted virus. However, the pathogenicity of other viruses such as potato Y virus, tobacco rattle virus, alfalfa mosaic virus and cherry leaf roll virus were unaffected in these plants.

We have begun to investigate the mode of action of resistance achieved in the SLRSV transformed plants. The capsid protein of SLRSV consists of one small and one large subunit. They are formed in the infected plant cell following cleavage of a larger protein. We have transformed tobacco plants to contain either the small, the large subunit or the precursor protein. In nematode feeding experiments only the plants expressing the large subunit protein were resistant to SLRSV. The durability of protection in perennial horticultural crops which are most severely affected by SLRSV (e.g. raspberry and cherry), remains to be determined. Such work is proceeding in collaboration with scientists at Dundee. This work is supported by **the Department of the Environment** and **the Ministry of Agriculture, Fisheries and Food**.

Development of genetically engineered poplar to provide resistance to Poplar Mosaic Virus (PMV)

The entire genome of PMV has been cloned and sequenced. Analysis of the primary nucleotide sequence revealed six open reading frames (ORFs). ORF-1, located at the 5' terminus of the genome is a putative polymerase gene coding for a protein with three domains: a methyl-transferase, an NTPbinding/helicase and a core with a characteristic GDD motif. ORFs-2, -3 and -4 collectively form a "triple gene block" which, by analogy with such structures in other viruses, is thought to be involved with virus movement. ORF-5 encodes the 36K capsid protein. Only this product has been unambiguously identified in translation products of the virion-derived RNA. The PMV capsid protein contains the sequence motif (R/K)FA(G/A)FD-XFXXVXXXXAA which is

conserved in both carlaviruses and potexviruses. The 3' terminal ORF, which is overlapped by the capsid gene, encodes a 14K polypeptide containing a "zinc-finger" motif.

Experiments addressing the protective efficacy of PMV-derived sequences have involved preparing transgenic tobacco (*Nicotiana benthamiana*) containing a chimeric sequence that includes part of the PMV 14K protein fused to the capsid coding sequence. Of 10 lines shown to contain the viral DNA, Western transfer hybridisation revealed the capsid protein in eight. In the two remaining lines no capsid protein was detected. Four lines were resistant to infection by the homologous virus. There was no correlation between amounts of capsid protein expressed by the transgenic plants and resistance to PMV. To facilitate exploitation of such virus-derived resistance genes, 10 poplar genotypes of hybrid black poplar with commercial significance within the European Community have been established *in vitro* and gene delivery systems/regeneration protocols are being optimised. This work was supported by **the European Commission under projects in the FOREST and AIR programmes**.

Virus Ecology and Bio-control

J S Cory

One of the objectives of the research in the Virus Ecology and Bio-control group is to develop new forms of bio-control for insect pests. The loss of agricultural crops to pests continues, despite the widespread use of an armoury of chemical insecticides sold annually by the multi-billion dollar pesticide industry. This problem is exacerbated by the negative effects that many chemicals have on the environment and natural resources as well as human, animal and plant health. There is a need to develop new, effective and environmentally-compatible pesticides. One option for pest control is the use of naturally occurring micro-organisms (biopesticides), as well as those enhanced by recombinant DNA technology. Genes from members of one phyla can be incorporated into members of another creating novel combinations and providing new generations of genetically engineered pesticides to join the battle against pests.

First field trial of a genetically improved virus insecticide

One area of pest control which has attracted particular attention worldwide is the genetic modification of bioinsecticides, in particular the insect baculoviruses. Baculoviruses are a group of large DNA viruses which only infect arthropods (primarily, insects). They are particularly common in Lepidoptera. However, unlike synthetic chemical insecticides, they are much more specific, infecting only a limited number of species. The plant-feeding larval stages of particular insect species are susceptible to certain types of baculoviruses, which they ingest whilst feeding or browsing on foliage. Following death of a susceptible larva, the virus-filled cadavers (Figure 1) eventually lyse, releasing large quantities of virus which provide a source of inoculum for other susceptible larvae. Birds, rodents and other invertebrates, although themselves uninfected by the virus, are often involved in the passive spread of virus in the environment.

In terms of their capacity to reduce crop damage by insect feeding, the most successful genetically engineered baculoviruses identified in the laboratory to-date are those which express insect-selective toxins derived from other species (e.g., one of the cocktail of toxins produced by scorpions, or a toxin of mites etc).

***Figure 1**: Pine beauty moth larva, killed by a baculovirus. The larva is much paler than an equivalent-aged healthy larva because of the large number of virus occlusion bodies showing through the weakened cuticle.*

To validate the laboratory data, permission was granted to IVEM in 1993 for the first field trial anywhere in the world of an improved genetically engineered baculovirus (i.e., the one prepared by IVEM that produces an insect selective scorpion toxin; Stewart et al., 1991, Nature **352**, 85). The main aim of the trial was to see if treatment with the recombinant virus would reduce crop

Figure 2 *(a)*

Figure 2 *(b)*

Figure 2 *(c)*

Figure 2*: Damage to cabbage plants in a) control plots infested with healthy cabbage looper Trichoplusia ni larvae; b) similar plots treated with a high dose of wild-type virus (10^8 PIBs/m^2); or c) a similar dose of recombinant virus.*
Pictures taken 16 days after virus application.

damage produced by caterpillars feeding on cabbage. The results showed conclusively (Figure 2) that caterpillar damage to the cabbage plants was significantly lower in the plots treated with virus expressing the scorpion toxin than in the plots treated with the wild-type virus (Cory *et al.*, 1994, Nature **370**, 138). This important result paves the way for the further development of insecticides which can be designed to be more compatible with environmental needs than the currently available chemical pesticides.

Further trials are underway to investigate virus persistence and the fitness of genetically engineered baculoviruses as well field studies on the effects of baculoviruses on less susceptible host species.

Studies of iridoviruses: proposals for a new classification scheme

Iridescent viruses (IVs) are large icosahedral viruses, 130-200 nm in diameter containing a DNA genome. Insects and other invertebrates infected by these viruses often display a vivid blue-green opalescence which has been the key criterion in the past for diagnosing IV infections. However, such remarkable symptoms are extremely rare in most susceptible host populations. Studies at IVEM have demonstrated that the incidence of covert (nonlethal) infection by IVs can be orders of magnitude higher than the overt (lethal) form in populations of blackflies (Diptera: Simuliidae), which are important vectors of human disease, particularly onchocerciasis. On the basis of these results, the importance of IVs as invertebrate pathogens and as potential control agents for insect pests may be considerably different from the established view.

DNA and other studies undertaken at IVEM have led to a new classification for IVs that is under consideration by the International Committee for Taxonomy of Viruses (Williams and Cory, 1994, J. Gen. Virol. **75**, 1291).

Flaviviruses

E A Gould

The purpose of the research is to understand the infectious and replicative processes of the arthropod-transmitted flaviviruses in both their vectors and vertebrate hosts and to identify the factors that determine their pathogenetic characteristics.

Underpinning this work is the production of infectious cDNA clones which can be characterised and modified by mutation and gene exchange experiments. The effects of such modifications will be examined in both vertebrate and invertebrate hosts. The work is focused primarily on the tick-borne flaviviruses (including those in the UK). Complementary contract and grant supported research using genetic engineering and immunological procedures involves veterinary, medical and ecological aspects of flavivirus diseases.

Development of infectious cDNA clones to study flavivirus replication and pathogenesis and virus control methods

Louping ill (LI) and tick-borne encephalitis (TBE) viruses are closely related tick-borne flaviviruses that naturally infect a wide variety of vertebrate species including wildlife, livestock and on occasion, humans. The entire nucleotide sequences of representative strains of both viruses have been determined and used to assemble full-length cDNA copies of the viral RNA genomes. RNA transcripts of these cDNA molecules are being produced to isolate infectious virus clones. Once accomplished, it will be possible to engineer precise changes into the virus genome and by gene exchange experiments, produce chimaeric viruses. Genetically modified viruses will be analysed to determine the genes and sequences involved in tick-vector competence and virus neurotropism in vertebrate species. cDNA-derived chimaeric viruses will also have application to the development of vaccines for livestock and humans.

Characterisation of recombinant viruses expressing the PrM/E genes of selected flaviviruses

Baculovirus expression vectors have been developed to prepare individual and combinations of proteins encoded by the flavivirus RNA genome. Although flaviviruses are antigenically closely related they also exhibit antigenic differences (Gould, *et al.*, 1985, Journal of General Virology **66**, 1369). These differences can be exploited to develop diagnostic systems. With support from **the Ministry of Defence**, and in order to develop rapid and sensitive systems for discriminating between flaviviruses, recombinant baculoviruses that express the pre-membrane and envelope (PrM/E) genes of selected flaviviruses have been produced. The purified recombinant proteins have been used to develop rapid diagnostic systems. The expressed proteins form non-infectious, virus-like particles which are under investigation as candidate vaccines.

Use of immunological methods to study flavivirus pathogenicity

To support the studies on flavivirus replication, pathogenicity, and host defence mechanisms we need to understand the nature of virus-antibody interactions. This can be achieved by developing genetically engineered monoclonal antibodies that exhibit the same functions as conventionally derived monoclonal antibodies. With support from **Centocor Inc** and **the Ministry of Defence**, we have engineered a monoclonal antibody that neutralises LI and TBE virus infectivity. The engineered antibody has been expressed via an infectious cDNA clone of Sindbis virus. Recombinant Sindbis virus infected cells resist infection with LI virus due to the presence of the intracellular antibody to LI virus. The system has the potential to produce purpose designed viruses that can control diseases in vertebrates.

In parallel work, techniques have been developed to produce phage libraries of random sequence peptides. These libraries

are being used to map monoclonal antibodies against tick-borne flaviviruses. Peptide sequences that bind neutralising monoclonal antibodies will be tested for their potential as immunising agents against the appropriate flaviviruses. Peptide sequences that bind monoclonal antibodies with particular virus specificities will be assessed for their potential in rapid diagnosis kits.

Tick-borne flavivirus evolution: demonstration of a cline across the northern hemisphere

With support from **the Chinese Government, the British Council** and **the Ministry of Defence** we have determined the nucleotide and primary amino acid sequences of the envelope (E) gene of a number of tick-borne flaviviruses. Equivalent sequence data are available in databases for many of the mosquito-borne flaviviruses. A phylogenetic analysis of these data has been made to provide a rational scheme of classification for the genus Flavivirus. From the data the following conclusions have been made: 1) the tick-borne flaviviruses have evolved as a "genetic continuum" or cline, 2) the various genes have evolved at comparable rates, 3) site mutations that arise as the result of positive selection have been identified, 4) the E gene alone is a valid genetic marker of each virus species, 5) a critical analysis of the E gene data shows that there is a relationship between genetic and geographic distance within the tick-borne flaviviruses. Our results provide us with a unique model with which to study the distribution and evolution of viruses in the natural environment.

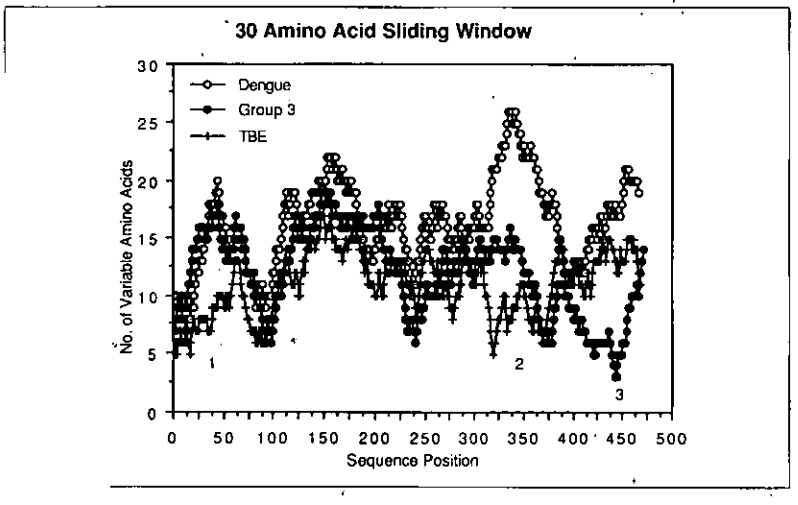


***Figure 1**: Comparative 30 amino acid sliding window analysis of the E proteins from tick-borne, JE-related (referred to as Group 3) and DEN serogroup viruses. The numbers 1, 2 and 3 on the graph denote the positions of maximum difference in variability between TBE complex and the DEN serogroup viruses.*

Epidemiology of LI infections

Sheep are regarded as the major amplifying hosts of LI virus in certain regions of the UK. Acaricides and vaccines are used to control ticks and LI virus infections of sheep. However, the virus causes high mortality amongst grouse populations on upland estates in Scotland. A one tube method has been developed to identify the presence of LI or TBE viruses in tick samples. It involves reverse transcription (RT) and polymerase chain reaction (PCR) using the RNA in LI or TBE virus-infected ticks. Individual virus species are identified within 48 hours of collecting the field sample. In parallel investigations, we have produced, characterised and used monoclonal antibodies with defined specificity to identify LI virus antigen in the same tick samples.

Classically, Louping ill is a major problem in the upland sheep grazing regions of Scotland, Northern England, as well as Wales and south-west England. This is largely because sheep are important in sustaining tick populations and because they produce large quantities of virus which are transmitted to ticks when they take a bloodmeal. Our research has shown that other vertebrate hosts are also involved. Using procedures described above, we have demonstrated that ticks removed from mountain hares in LI virus enzootic areas in Scotland are infected with the virus. Experimental evidence has been obtained that the mountain hares can transmit LI virus between ticks as they co-feed even in the presence of neutralizing antibody.

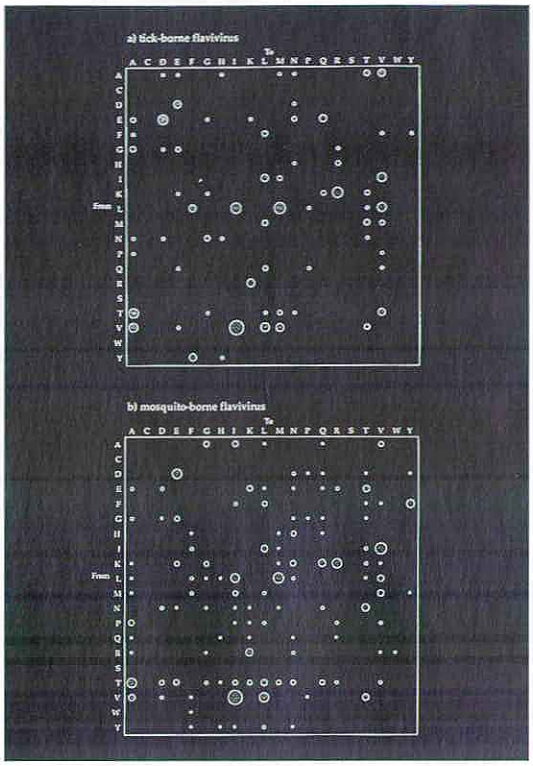


***Figure 2**: Comparative analysis of the tick-borne (upper) and mosquito-borne flavivirus envelope sequences. The figure depicts amino acid substitutions ("from" on the x axis and "to" the y axis). The dot size indicates the frequency of substitution of each amino acid (largest dot = most frequently substituted). The frequency reflects the constraints imposed on the protein by its structure.*

***Figure 3**: Mountain hare with engorged adult tick attached.*

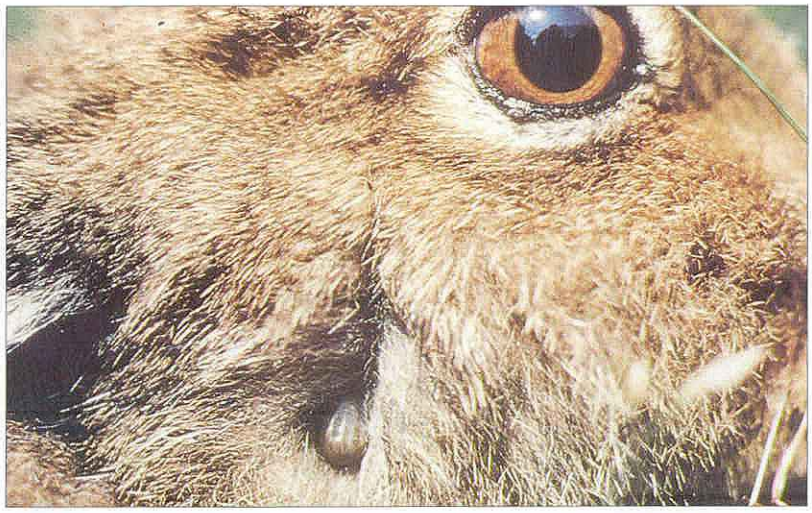


***Figure 4**: Red grouse.
Is the decline in the survival of chicks related to the presence of louping ill virus?*

Virus Protein Functions

I M Jones

Virus life cycles are intricate and involve a cascade of events that ultimately leads to the generation of new virus particles. In such infections, the contribution of any one viral protein to the overall process is often difficult to assess because subsequent effects are not necessarily associated with the primary function of the protein. In many cases much can be learnt by the production of the target protein in isolation. The baculovirus expression system has been widely used for this purpose. In this group we seek to develop further and exploit the baculovirus system to understand the functions of virus proteins in areas of virology that are important, scientifically challenging and potentially exploitable. By dissecting the molecular basis of virus protein function, the rational design of vaccines and antiviral drugs becomes possible.

New vectors for old problems

Recombinant baculoviruses continue to be widely used for the expression of proteins of commercial and academic importance. The proteins are expressed in insect cells following infection with a recombinant baculovirus and may be harvested after two or three days of infection. For many proteins the level of expression is such that purification of the protein is easily achieved and with a high yield. However, in cases where protein expression is sub-optimal, purification of sufficient protein is often a major hurdle. To overcome this problem a set of novel baculovirus expression vectors that incorporate affinity tags to provide a one step purification procedure have been developed. One affinity tag is glutathione-S-transferase (GST) which has a high affinity for reduced glutathione. Recombinant proteins fused to GST are purified on an immobilised glutathione support and eluted in purified form by washing with reduced glutathione. The vectors devised incorporate a number of features to aid subsequent manipulation (see Figure 1).

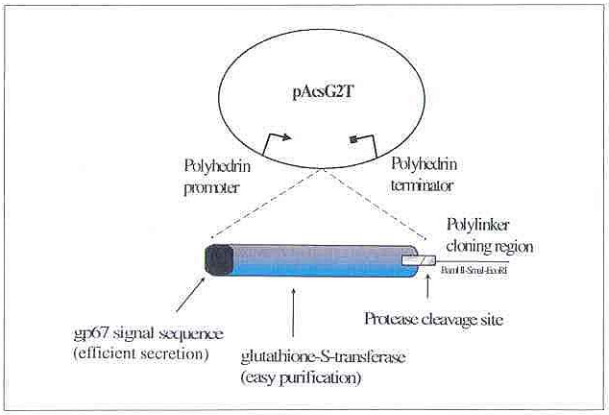


***Figure 1**: The genetic map of transfer vector pAcG2T. Genes cloned into the polylinker site are fused to the protein GST and can be purified in a single step from insect cells as shown in Figure 2.*

These include a variety of restriction sites for the introduction of cloned DNA fragments, a site-specific protease cleavage sequence situated between the GST domain and the cloned protein to allow removal of the affinity tag following protein purification, and the addition of a glycoprotein signal sequence at the amino terminus of GST to facilitate secretion of the fusion protein from infected insect cells. An example of the efficiency of the new vector system is shown in Figure 2 where, with support from **the Medical Research Council**, the major surface glycoprotein of HIV has been expressed as a

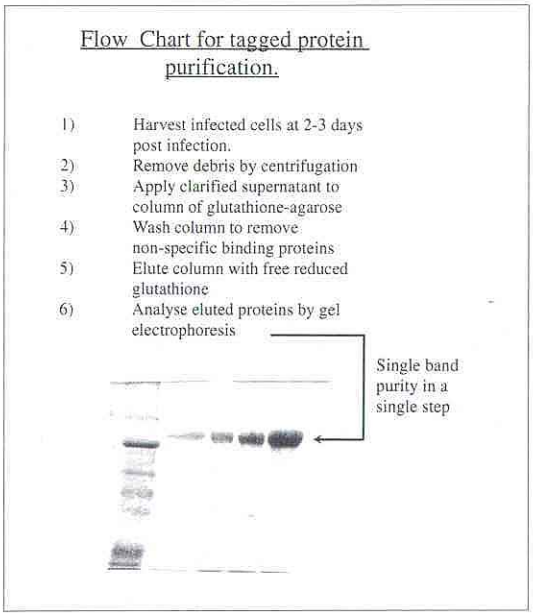


***Figure 2**: A typical flow chart for the purification of a GST fusion protein produced by the transfer vectors described in Figure 1 and a typical gel analysis of the result showing a homogeneous preparation of purified protein.*

fusion with GST and purified in a single step from the supernatant of infected cells. The complete protocol can be completed within a day, far faster than by other procedures. Since no harsh conditions are employed, the proteins maintain their full biological activity. The vectors and the products produced by them have been licensed to a number of biotechnology companies for sale.

HIV virus assembly

As the causative agent of AIDS, HIV continues to be a major focus for virus research worldwide. One area of promise for therapeutic intervention is virus assembly. With support from **the Medical Research Council**, recombinant baculoviruses have been developed to study the process of HIV assembly. The expression of the major virus structural protein (Gag) leads to assembly of a virus-like particle (VLP) similar in size and morphology to the authentic HIV virion (Figure 3). Mutation of the *gag* gene followed by re-expression of the mutant protein has permitted us to generate a physical map of the residues that are important for VLP assembly. An example is shown in Figure 4 where four amino acid residues within the p17 domain of the *gag* gene have been changed: cysteine-57 to serine; leucine-64 to alanine; leucine-78 to alanine; cysteine-87 to serine. Analysis of the VLPs produced in infected insect cells following expression of these mutants demonstrated that the identity of two of these four amino acids is critical for the process of VLP assembly. The three-dimensional structure of this section of the Gag protein is available and shows the critical residues are located in a single alpha helix on one side of the molecule (Figure 5). It is likely that helix-helix interactions occur between monomer molecules that lead to the ordered assembly of subunits required to form a VLP. Further use of this system to complete the map of residues important for virus assembly will allow this hypothesis to be confirmed.

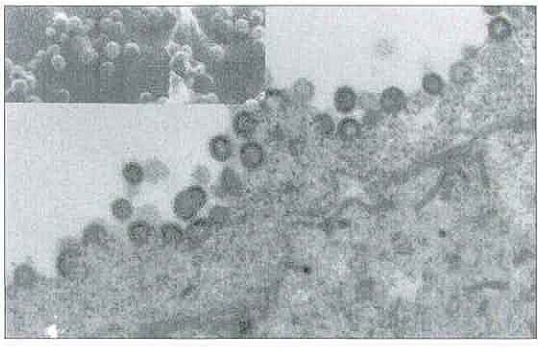


***Figure 3**: Electron micrographs of the production of HIV VLPs in insect cells following expression of the major core protein Gag p55 using recombinant baculoviruses. The cells were visualised at two days post-infection. The main panel shows a section through an infected cell with many VLPs budding through the cell plasma membrane whilst the inset shows a scan of the cell surface.*

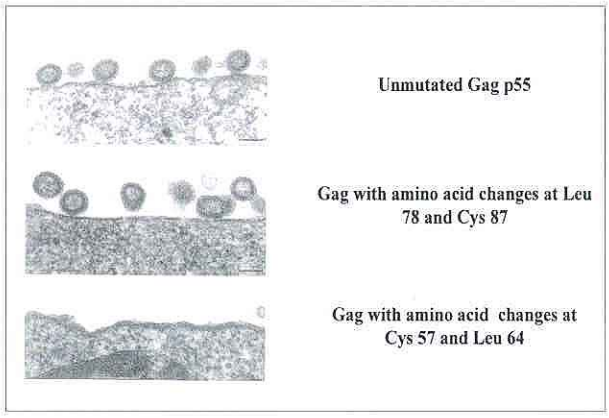


***Figure 4**: Analysis of Gag p55 mutants. Infected cells were fixed at two days post-infection and processed for electron microscopy. The figure represents typical fields observed for each mutant. Neither Cys 57 or Leu 64 showed evidence of VLPs forming, instead, a layer of Gag antigen was present beneath the membrane. Mutation at Leu 78 and Cys 87, had no effect on particle formation.*

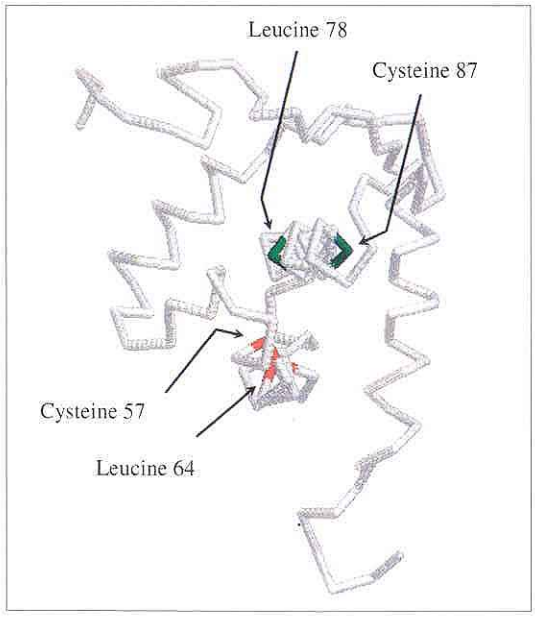


***Figure 5**: The three-dimensional structure of the p17 domain of Gag p55 showing the location of the mutations that inactivate VLP assembly.*

Tick-borne Pathogens

P A Nuttall

The mission of the group is to define the interactions between ticks, vertebrate hosts and the pathogens (viruses and bacteria) they transmit. The results are used to develop diagnostic tests, risk assessments, therapeutic reagents and vaccines.

Tick-borne virus ecology and evolution

With support from a NERC Special Topic studentship and in collaboration with ITE Banchory, we are examining the effect of ticks and tick-borne viruses on seabirds breeding on the Isle of May, Scotland. The most abundant seabird tick is the ixodid species, *Ixodes uriae*. Eighteen orbiviruses have been isolated from 219 individually-examined ticks. Each isolate is unique in that it shows a distinct gel migration pattern of the 10 double-stranded RNA segments comprising the viral genome. The remarkable degree of genetic variability suggests either a high rate of evolution of tick-borne orbiviruses on the island, or a high degree of recruitment of such viruses from other seabird colonies via infected seabirds or seabirds carrying infected ticks.

With support from **the European Community** joint studies with groups in Senegal and Greece revealed a similar situation for Crimean-Congo haemorrhagic fever (CCHF) virus. This zoonotic tick-borne virus is found in Africa, Asia, and Europe. A dendrogram based on sequence analyses of the small viral RNA segment showed the Greek isolate to be the most genetically divergent, indicating ecological isolation. In contrast, isolates from Africa and Asia were inter-related suggesting gene flow which may result from virus dissemination via birds, a primary host of the tick vectors of CCHF virus.

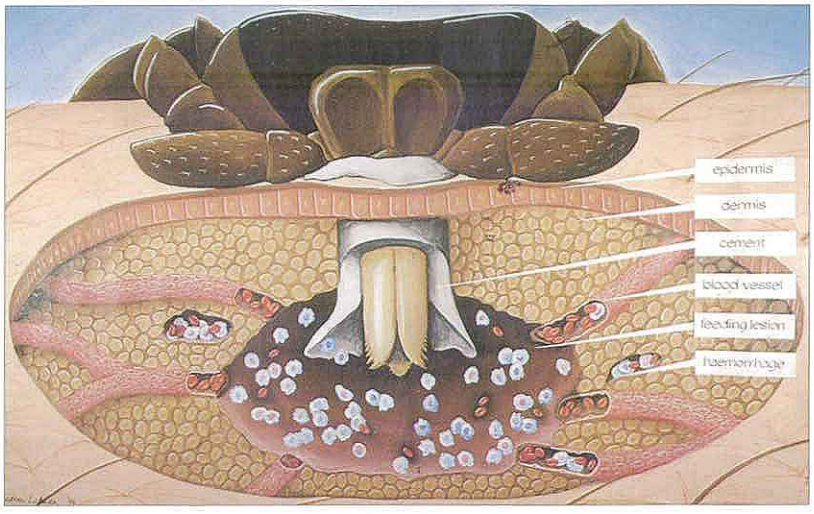


***Figure 1**: Schematic diagram showing a tick attached to the skin of its host and the substrates on which the tick feeds. Products secreted by the tick into the feeding site facilitate the uptake of blood and modulate the host immune response.*

Role of tick saliva in virus transmission

During the prolonged feeding period of ticks on their hosts, bioactive proteins are secreted in tick saliva to facilitate the uptake of blood (Figure 1). Several tick-transmitted viruses exploit the effects of these salivary gland components to promote virus transmission. In collaboration with groups in Slovakia and Japan and with support from **Pitman-Moore Ltd**, we have investigated the mechanism of this "saliva-activated transmission" (SAT). Our studies have shown that salivary gland products suppress natural killer cell activity, reduce mRNA expression of nine different cytokines, and bind to host IgG. Such powerful immunomodulatory effects of ticks at the skin site of tick feeding may aid virus transmission by inhibiting the local host immune response to virus infection.

Ecology and bio-diversity of *Borrelia burgdorferi*

B. burgdorferi sensu lato is the causative agent of a borreliosis that affects humans and certain domesticated animals in Europe and North America (e.g., Lyme disease). Small mammals are considered to be the principal natural host of this tick-borne spirochaete and control measures have been designed accordingly. Our combined studies with the University of Oxford showed that, in UK woodland habitats, grey squirrels and pheasants are more important than field mice

and bank voles as hosts of *B. burgdorferi*. The ecological diversity of the spirochaete in the UK is reflected in the apparent bio-diversity of the organism. Supported by **the Health and Safety Executive** we showed by comparisons of chromosomal macrorestriction fragments that greater similarity exists between two so-called "genospecies" of European *Borrelia* spirochaetes than between three UK isolates (two from the New Forest region and one from Thetford Forest). Whether the vaccines being developed from American and continental European isolates will be efficacious against the UK species will need to be determined.

Screening over 400 tick samples supplied by an *ad hoc* group of collectors across the UK and using a polymerase chain reaction protocol that has been established to identify *B. burgdorferi* in tick extracts, has confirmed that *Ixodes ricinus*, the common sheep tick, is the most important potential vector of the pathogen in the UK (Figure 2). Other tick species, including the hedgehog tick (*I. hexagonus*) and the seabird tick (*I. uriae*) can also be infected (Figure 2). The distribution of ticks identified as harbouring *B. burgdorferi* is being mapped in collaboration with the Biological Records Centre, ITE Monkswood..

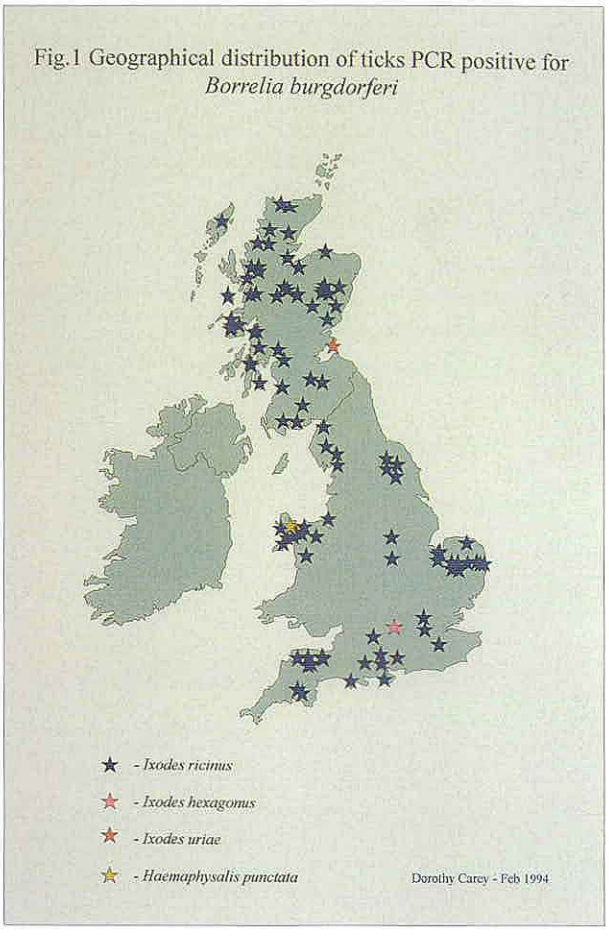


***Figure 2**: Distribution of ticks infected with B. burgdorferi spirochaetes as determined by the polymerase chain reaction.*

Molecular Biology of Baculoviruses

R D Possee

The questions under study are how baculoviruses replicate in insect cells and, using genetic engineering, how this may be exploited to develop improved insecticides and the baculovirus expression system. Baculoviruses are insect-specific pathogens that may be used both as biological pesticides to replace chemical agents, and as vectors for the expression of foreign genes. Underpinning the work are efforts to understand baculovirus gene function with the aim of producing improved, genetically engineered virus insecticides and more efficient expression vectors. Selected examples of these applications are presented below.

From genotype to phenotype: a case study

We have recently determined the complete nucleotide sequence of the baculovirus, *Autographa californica* nuclear polyhedrosis virus (AcNPV) (Ayres *et al.*, 1994, Virology **202**: 586). This now provides a base to understand the genetics of an insect-specific pathogen. Comparison of the virus genes with existing sequence libraries (GENBANK and EMBL) has identified a number of genes with similarities to those of other organisms. An example is an AcNPV chitinase gene and another with similarity to a cysteine protease. Deleting either or both genes from AcNPV has shown that they dictate whether or not a virus-infected caterpillar liquefies after death (Figure 1). The liquefaction process aids release of virus from the cadaver and increases the opportunity for the virus to spread the infection to other caterpillars.

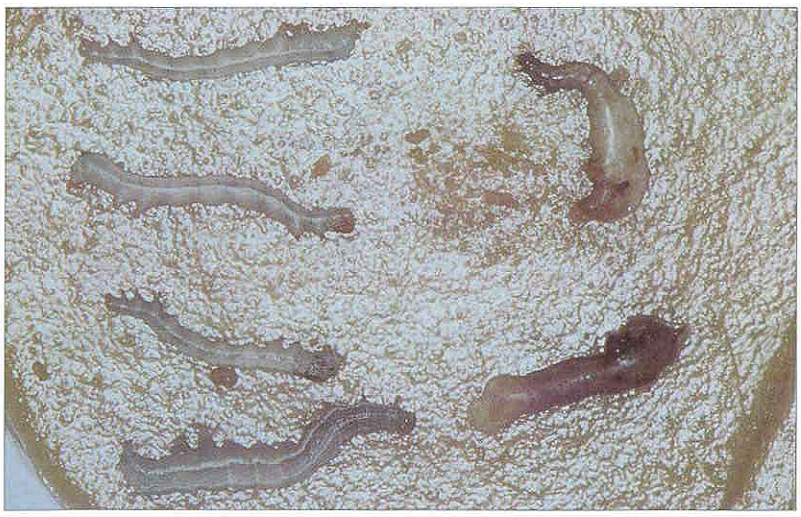


***Figure 1**: Liquefaction of virus-infected cells. Trichoplusia ni larvae infected with: (right) unmodified AcNPV; (left, top to bottom), AcNPV lacking both chitinase and cathepsin genes; AcNPV lacking the cathepsin gene; AcNPV lacking the chitinase gene; uninfected larva. Note the general disintegration of the insects in the top row in contrast with the retention of structural integrity of insects infected with the virus mutants in the bottom row.*

Using "genetic switches" to control baculovirus gene expression

While some virus genes can be directly modified or simply deleted from the baculovirus genome without affecting virus replication, alteration of essential virus genes is not as straight-forward. With support from **Pfizer Ltd** we have developed methods which circumvent this problem. Inducible genetic elements or "genetic switches" from bacteria have been introduced into the AcNPV genome to study the regulation of virus genes. In this system the expression of such genes is now only possible when a chemical inducer is present in the virus-infected cells. Removal of the inducer turns off expression. This system permits detailed analysis of the functions of such genes. This work has a valuable application in the use of baculoviruses as expression vectors of foreign genes. Foreign gene expression can be regulated, ensuring that even proteins toxic to insect cells can be manufactured.

Insect cells commit suicide!

Insect cells recognise that they are infected by baculoviruses very early in the replication process (a few hours after infection) and respond by committing suicide. This inhibits virus replication. The phenomenon is known as programmed cell death or apoptosis. Some viruses, such as AcNPV, counter apoptosis by expressing genes which

neutralise the suicide mechanism and allow virus replication to continue. Two AcNPV genes (p35 and IAP1) have been implicated in this process to-date by other workers in the field. Our analysis of the AcNPV genome has identified a third gene (IAP2). An interesting aspect of these observations is that the expression of the anti-suicide genes may have a role in determining the host range of baculoviruses. It has long been a mystery why baculoviruses can only grow in a small number of insect species. Early results, with support from **Zeneca Agrochemicals (Zeneca Ltd)**, suggest that it may be possible to limit the host range of genetically modified baculoviruses. We are currently searching for homologues of these genes in other baculoviruses to confirm their roles in regulating apoptosis and host range.

Genetically modified virus insecticides: the next generation

As reported elsewhere, the world leading research at IVEM has seen the first field trials with a genetically modified baculovirus (AcNPV) containing an insect-specific scorpion toxin gene. The work was supported by funds from **Wellcome Environmental Health (Wellcome Foundation Ltd)**, now part of **Roussel-Uclaf S.A.** This virus is unsuitable for the control of some insect pests, due to its limited effective host range. We are working in collaboration with **Zeneca Agrochemicals** to develop other insecticides for other insect pests, including the preparation of genetically engineered derivatives. Novel viruses have been isolated in the field and are now being characterised in the laboratory.

Orbiviruses

P Roy

The research concerns developing an overall picture and understanding of the virus assembly and morphogenetic pathways of selected complex RNA viruses of wild-life and veterinary importance using experimentally manipulated viral genes and gene expression systems. To achieve these goals novel baculovirus multiple gene expression vectors have been developed. The viruses under study include bluetongue virus (BTV), African horse sickness virus (AHSV) and epizootic haemorrhagic disease virus (EHDV) of deer. The analyses have involved X-ray crystallography of viral proteins (in collaboration with Dr D I Stuart, Oxford University), cryoelectron microscopy of viruses, their cores and morphological intermediates (in conjunction with Dr T F Booth and others), in addition to gene and protein engineering.

Development of baculovirus dual, triple, quadruple and quintuple expression vectors

To facilitate co-expression of the genes required to form surrogate virus cores and virions, multigene transfer and expression vectors have been prepared to co-express, two, three, four, or five foreign genes from the same recombinant virus. Certain of the transfer vectors have been licensed for sale by commercial companies.

Assembly of BTV multiprotein capsids

The BTV particle (84nm in diameter) contains 7 structural proteins organised into 2 protein shells and consisting of 4 layers. The innermost shell (the core) is icosahedral and involves VP7 (38 kDa, outer layer, 260 trimers) and VP3 (103 kDa, inner layer, 24 pentamers) that encapsidate the 10-segment, double-stranded (ds)RNA genome and 3 minor proteins: VP1 (150 kDa), VP4 (76 kDa), and VP6 (36 kDa). In virus particles the core is enclosed by an outer protein shell containing VP2 (110 kDa outermost, 180 copies) and VP5 (59 kDa innermost, 120 copies).

Each BTV dsRNA segment, except S10, encodes a single polypeptide. In addition to the 7 structural proteins, there are 4 non-structural (NS) proteins, NS1, NS2, NS3 and NS3A, that are made in BTV-infected cells. Of these, NS3 and NS3A are two related products of the S10 gene. cDNA clones representing all 10 dsRNA species of one BTV serotype (BTV-10) and those of certain other BTV serotypes, AHSV and EHDV have been prepared and expressed using baculovirus vectors to allow the attributes of the encoded proteins to be defined.

Using baculovirus multigene expression vectors BTV core-like particles (CLPs, VP3, VP7; including combinations with the minor proteins) have been prepared and analysed. Further, virus-like particles (VLPs) containing VP2 and VP5 in addition to the CLP proteins, have been made and characterised (see the Virus Ultrastructure Report).

The system has been exploited to investigate protein-protein interactions by creating mutant forms of selected BTV proteins, and by investigating their involvement in CLP and VLP assembly. For example, a series of deletion, extension, substitution and site-directed mutants of VP7 have been made and analysed. Among other results, the data have shown that a single lysine residue in VP7 (K_{255}); that is conserved among BTV serotypes, is obligatory for CLP formation. The various results have been correlated with the atomic structure of VP7 (see below). Similar studies have been conducted with VP3. The work has been supported by grants from **the Medical Research Council**.
Apart from the structural studies, a number of additional investigations have shown that both VP7 and VP3 proteins are suitable for the formation of chimaeric CLPs that provide a foreign immunogen delivery system.
The immunogen delivery work has been supported by grants and contracts from **the European Community** and **Oravax Inc**.

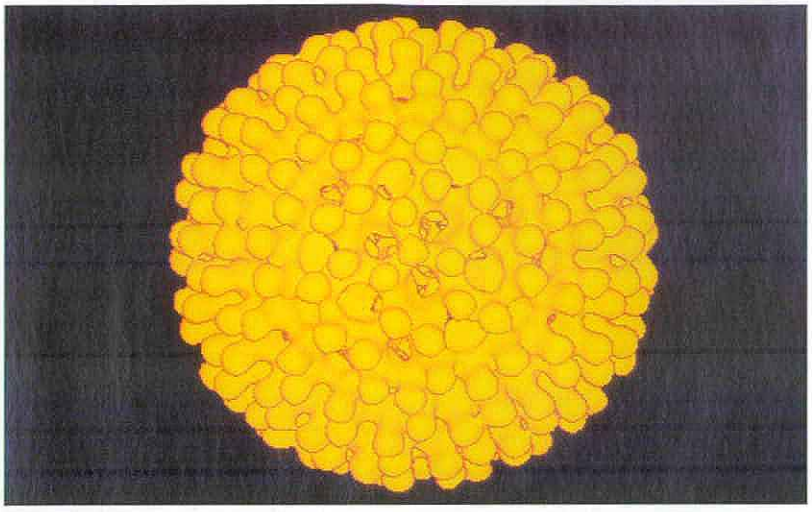
Three-dimensional structure of BTV VP7 trimers at the atomic level

The three-dimensional structure of baculovirus expressed VP7 trimers has been determined in collaboration with Dr D I Stuart (to 2Å resolution). VP7 has a molecular architecture not seen previously among viral proteins. Each VP7 subunit of the trimeric molecule (Figure 1) consists of two domains, one representing the top and composed principally of β-sheets, the other, located underneath, involving mainly a bundle of α helices. Each subunit has a short C-terminal arm which may tie trimers together during capsid formation. A concentration of methionine residues and other groups suggests that greasy lubrication may facilitate VP7 interactions in the trimers. This work is supported by grants from **the Medical Research Council** and **the Agriculture and Food Research Council** (now **BBSRC**).

Mapping functional domains of the non-structural proteins

The cytoplasm of BTV infected cells is characterised by the presence of large numbers of fibrillar virus inclusion bodies (VIBs) composed of the 41 kDa NS2 protein, as well as virus-specific tubules composed of multiple copies of the 64 kDa NS1 protein. Using protein engineering and baculovirus expression vectors, certain amino acids and sequences responsible for NS1 polymerisation have been identified using deletion and site-directed mutagenesis. The use of chimaeric NS1 to act as an immunogen delivery systems involving easily-purified tubules is under investigation.

The BTV NS2 protein is involved in the recruitment of viral mRNA transcripts for encapsidation and formation of the viral dsRNA genome. Domains and specific residues of the protein that are important in this function and those that are involved in oligomerisation have been identified by deletion mutagenesis and RNA binding studies.



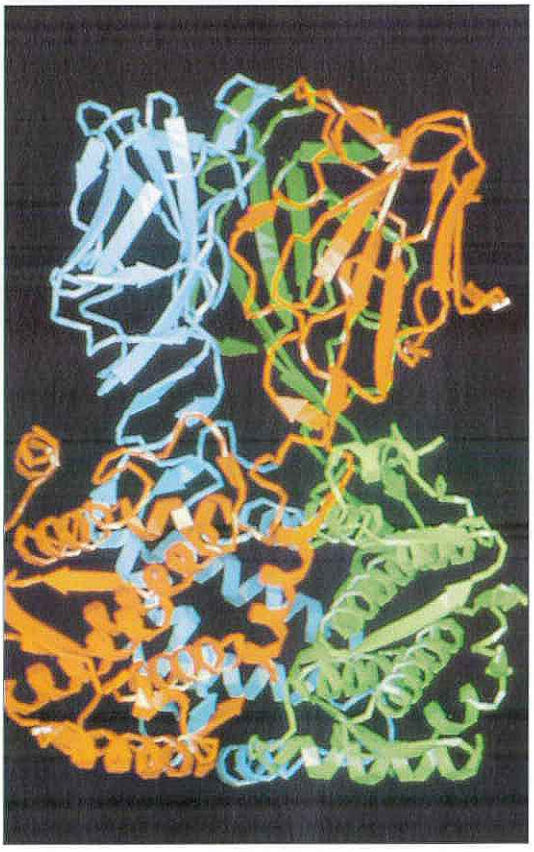


***Figure 1**: In the top panel is shown a BTV core particle at 28Å resolution. In the lower panel is shown the BTV VP7 trimer that represents one of the knobs of the core particle.*

Using a T7 mammalian transient expression system we have demonstrated that the NS3/NS3A proteins (24 to 26 kDa) are glycosylated and further modified by heterogeneous extension to

polylactosaminoglycan forms. The proteins are associated with cellular membranes and involved in the budding and extrusion processes of BTV from virus infected cells. Different aspects of the work on NS proteins are supported by grants from **the Medical Research Council, the Agriculture and Food Research Council (BBSRC)** and **Oravax Inc**.

Protective immune responses of baculovirus expressed BTV and AHSV proteins, VLPs and CLPs

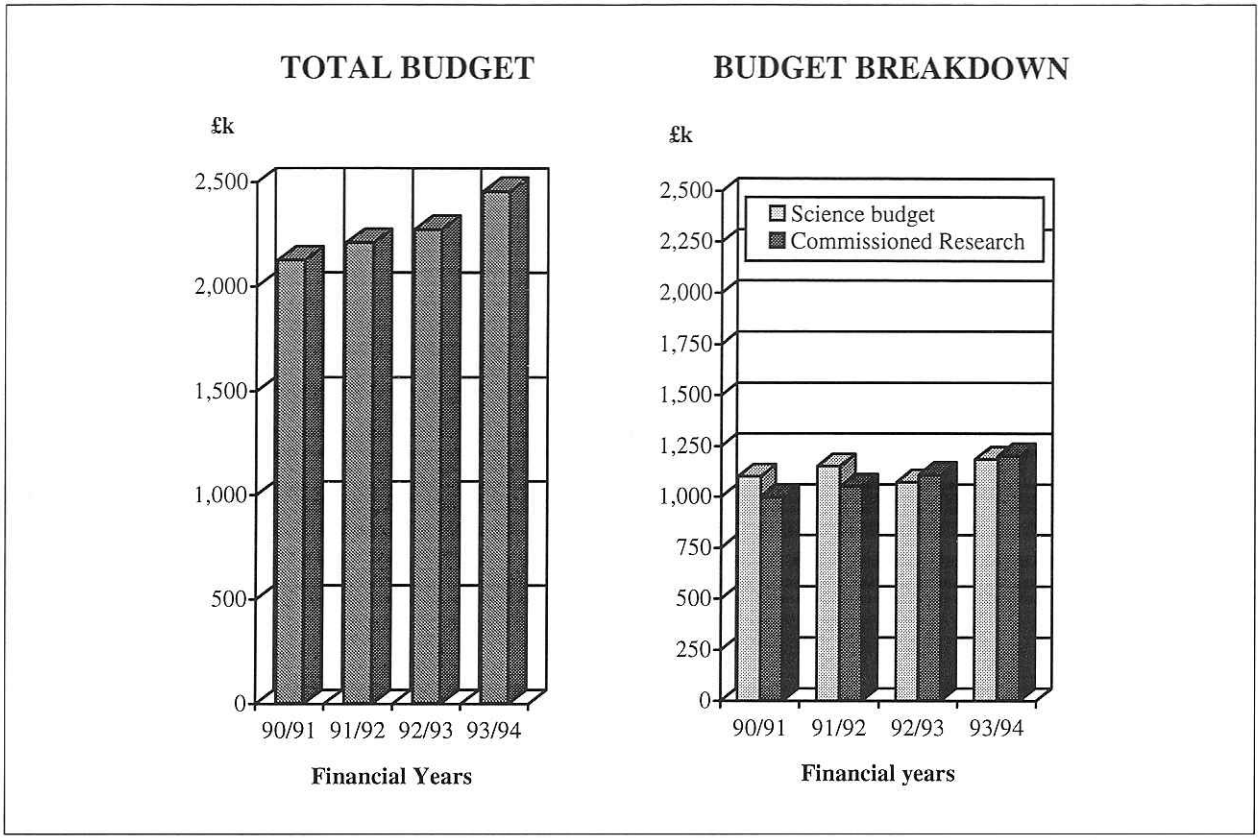
We previously demonstrated that baculovirus-expressed BTV VP2 alone elicits neutralising antibodies in sheep and provides protection against virulent challenge by the homologous virus. Since VLPs elicit higher titers of neutralising antibodies in guinea pigs than VP2 alone (or VP2 and VP5 combinations), VLPs have been tested as vaccines for sheep in collaboration with scientists and support from the **Onderstepoort Veterinary Research Institute** (Republic of South Africa) and, for trials in Townsville (Australia), **the Australian Woolgrowers Association**. The data have shown that the VLPs provide superior and long term protection (>15 months) following 2 vaccinations with 10 μg of VLPs. In certain cases, partial protection was afforded against challenge by heterologous BTV serotypes.

The serotype-specific VP2 protein of BTV and VLPs is considered to be the main antigen responsible for inducing virus neutralising responses in vaccinated animals. The roles of other antigens in procuring a protective immune response for BTV, such as those involving cell mediated responses, are not known. To investigate this issue we initiated a study in sheep using CLPs to determine whether they elicit protection, specifically cross-protection since the VP3 and VP7 antigens are highly conserved. Preliminary data indicate that the CLPs provided a partial protection in sheep against homologous and certain heterologous BTV serotypes, suggesting that cellular immunity may play a role in the overall protection process.

A candidate vaccine for AHSV has also been developed and tested in conjunction with scientists and support from **the Onderstepoort Veterinary Research Institute** as well as **the European Community** and **the Instituto Nacional de Investigation Agraria** (Spain) and **Immunologia y Genetica Aplicada S.A.** (Spain). Preliminary data indicate that the AHSV recombinant VP2 protein elicits high neutralising antibodies in vaccinated horses that should provide protection against virulent virus challenge. The length of such protection is currently under study.

Appendix 1

Financial Background



Research contracts during 1992 - 94 were obtained from the following customers:

Agriculture and Food Research Council; Australian Woolgrowers Association; British Biotechnology Ltd; Centocor Inc; Commission of the European Communities; Department of the Environment; Glaxo Research and Development Ltd; Health and Safety Executive; Horticulture Research International; Instituto Nacional de Investigation Agraria; Immunologia Aplicada y Genetica S.A.; Laboratoires VIRBAC, France; Medical Research Council; Ministry of Agriculture, Fisheries and Food; Ministry of Defence; Onderstepoort Veterinary Research Institute; Oravax Inc, USA; Oxford Instruments (UK) Ltd; Pfizers Ltd; Pitman-Moore Ltd; The Wellcome Foundation Ltd; The Wellcome Trust; Zeneca Ltd.

Royalties were received from:

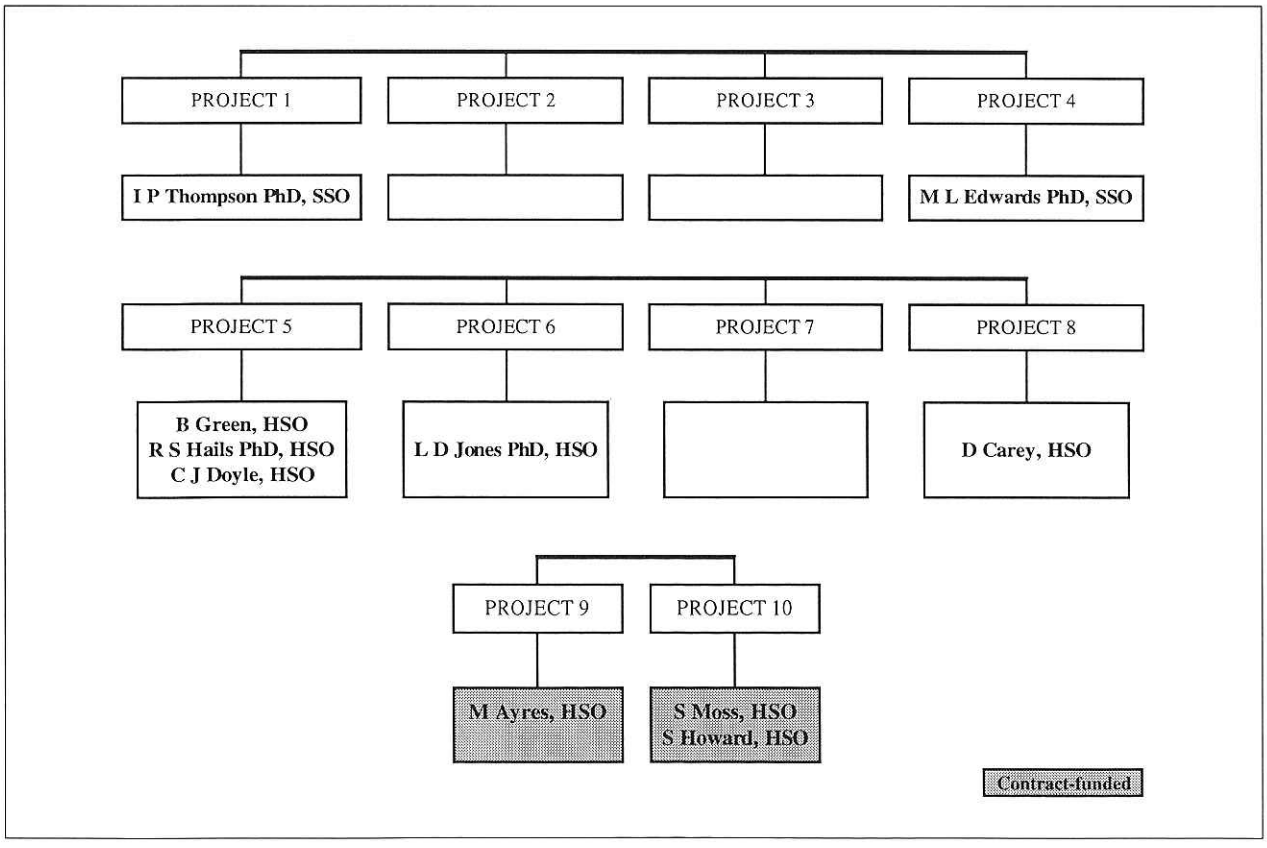
Clontech Inc, USA; PharMingen, USA.

Appendix 2

Organisation and Staff lists (as at October 1994)

Director				
D H L Bishop MA, DSc, FIBiol	1984 - present	UG5	Molecular Virology	Project 2
Assistant Director				
E A Gould PhD	1988 - present	UG6	Flaviviruses	Project 6
Project Leaders				
M J Bailey PhD	1987 - present	SSO	Microbial Ecology	Project 1
T F Booth PhD	1984 - present	SSO	Virus Ultrastructures	Project 3
J I Cooper PhD	1972 - present	UG7	Plant Virology	Project 4
J S Cory DPhil	1984 - present	SSO	Virus Ecology and Bio-control	Project 5
I M Jones PhD	1987 - present	UG7	Virus Protein Functions	Project 7
P A Nuttall PhD	1980 - present	UG7	Tick-borne Pathogens	Project 8
R D Possee PhD	1981 - present	UG7	Molecular Biology of Baculoviruses	Project 9
P Roy PhD	1986 - present	RSX	Orbiviruses	Project 10

Other Permanent Scientific Staff



Term Appointment

Scientific Staff			**Project**
A Belyaev PhD	1991 - 1993	HSO	10
T Bourner PhD	1989 - 1992	SO	5
A Buckley PhD	1988 - 1993	HSO	9
U Bhattacharyya PhD	1992 - 1995	SSO	7
Y Boublik PhD	1993 - 1994	HSO	7
P Bramwell PhD	1993 - 1994	HSO	1
S Butcher PhD	1992 - 1995	HSO	2
A Davies PhD	1989 - 1993	HSO	7
J Diaper PhD	1993 - 1996	HSO	1
C B Doyle	1990 - 1996	SO	7
R Ellis	1992 - 1994	SO	1
A Fleetwood	1991 - 1992	SO	7
M Gibbs	1991 - 1994	HSO	4
D Goulson PhD	1992 - 1994	HSO	5
T Gritsun PhD	1990 - 1995	HSO	6
I C Hauxwell	1989 - 1994	SO	5
W Hawes	1992 - 1994	HSO	4
J Henderson PhD	1992 - 1993	HSO	4
P Hernandez-Crespo PhD	1994 - 1995	HSO	5
M L Hirst	1987 - 1993	HSO	5
W Jiang	1990 - 1995	HSO	6
J Jowett DPhil	1989 - 1992	SO	7
H J Killick	1967 - 1992	UG6	5
N Kobayashi PhD	1989 - 1993	HSO	1
R Krykbaev PhD	1994 - 1997	HSO	7
M Labuda PhD	1991 - 1994	HSO	8
A Livesley PhD	1991 - 1994	HSO	8
A Lilley	1993 - 1996	HSO	1
M Lopez-Ferber PhD	1989 - 1992	HSO	9
Y Liu DPhil	1992 - 1995	HSO	4
S M Marin PhD	1993 - 1994	HSO	6
A C Marriott PhD	1987 - 1994	SSO	8
P McCormack PhD	1991 - 1993	HSO	1
A Merryweather-Clarke PhD	1988 - 1995	HSO	4
Y Morikawa PhD	1992 - 1992	SSO	7
M Niikura PhD	1992 - 1993	HSO	2
T Niikura	1992 - 1993	HSO	2
G Paesen PhD	1992 - 1995	HSO	8
B J Powell PhD	1989 - 1993	HSO	7
C Prehaud PhD	1989 - 1992	HSO	2
P Rainey PhD	1991 - 1994	HSO	1
O Rosenwasser	1993 - 1993	HSO	4
E Snezhkov PhD	1992 - 1994	HSO	2
G Spraggon DPhil	1993 - 1994	HSO	2
C Tiley	1991 - 1993	SO	5
K N Venugopal PhD	1989 - 1994	HSO	6
Y H Wang PhD	1993 - 1996	HSO	1
C Watkins DPhil	1989 - 1992	SO	7
C Williams	1993 - 1993	SO	10
T Williams PhD	1990 - 1994	HSO	5
W H Zhang	1993 - 1996	SO	7

Administrative and Support Staff

L M Atkinson	1988 - 1992	EO
R W Bateman	1992 - 1995	SGB2
C Broadbent	1994 - 1997	ASO
R Broadbent	1983 - present	PTO
T Carty	1980 - present	SO
K B Chaloner	1980 - 1994	SO
A C Forkner	1989 - 1994	TO
C D Hatton	1977 - present	Phot
P Henbest	1988 - present	SO
E Hodgson	1987 - 1993	SO
J C Jeacock	1990 - 1995	AO
B Lewis DPhil	1993 - 1996	EO(C)
R MacKenzie	1984 - present	PTO
D McCall	1976 - present	ASO
S Morton	1992 - 1996	SGB2
P Newton	1992 - 1996	SGB2
C Nobbs	1992 - 1992	PS
G Pinniger	1992 - 1996	SGB2
R Pinniger	1992 - 1996	SGB2
S Pinniger	1993 - 1996	PS
S Price	1989 - present	Typ
A A Primarolo	1981 - present	PTO
E Robins	1990 - 1992	Typ
J M Sloley	1991 - present	EO
A Sloper	1985 - present	SGB2
C Wilson	1993 - 1995	Asst Lib

Contractual and Short term workers

G F Bamford	1988 - 1995
F Fry	1989 - 1992
E Hemmings	1981 - 1993
C J Lawrence	1989 - 1995
M Tinson	1989 - 1993

Students		Project
A Barnett	1993 - present	9
M Bridges	1994 - present	2
S Chapple	1994 - present	9
B Chauhan	1993 - present	2
E Cleal	1994 - present	3
S Collins	1992 - present	5
N Craine DPhil	1990 - 1994	8
R Ellis	1994 - present	1
F Gao	1991 - present	6
M Gaunt	1992 - present	6
V Goddard	1994 - present	1
C Harrold	1991 - present	9
R Hawtin PhD	1990 - 1993	9
C Hill	1994 - present	3
N Horscroft	1994 - present	10
S Kreiah DPhil	1988 - 1993	4
M Leahy	1994 - present	8
A Lilley	1990 - 1994	1
K Monastyrskaya	1990 - present	10
M A Morse DPhil	1988 - 1993	8
M Nunn	1992 - present	8
N Ogden BVSc, MRCVS	1992 - present	8
R Paul	1991 - present	5
D F Phillips	1993 - present	2
I Polkinghorne	1991 - 1994	10
J Pullen	1988 - 1994	9
A Richards PhD	1989 - 1993	5
C Thomas	1993 - present	9
S Thompson	1991 - present	9
T Timms	1994 - present	1
V Urquidi DPhil	1988 - 1992	2
S Vasconcelos	1991 - present	5
H Wang	1991 - present	8
A Whitehouse	1991 - present	9
C Williams	1994 - present	10
K Wilson	1994 - present	5
D Wright	1994 - present	10
P Zanotto	1991 - present	9
H Zhang	1994 - present	1

Visiting Workers		Project
S Adams	1992 - 1993	10
C Argentini PhD	1990 - 1992	2
O Bansal PhD	1992 - 1994	10
A Basak PhD	1992 - 1995	10
S Braütigam PhD	1990 - 1992	2
A-R Ciccagiglione	1992 - 1992	7
H Gorham PhD	1993 - 1993	10
L Hongmei	1992 - 1993	10
J Kuzio PhD	1992 - 1994	9
L Li	1993 - 1993	9
P T Loudon PhD	1989 - 1992	10
J Martinez PhD	1992 - 1993	10
M Mikhailov PhD	1994 - 1997	10
C Parker PhD	1994 - 1997	2
A Peek	1994 - 1997	10
P Reay	1993 - 1996	10
J Rodriquez PhD	1994 - 1999	10
J Smith	1992 - 1994	10
N Staüber PhD	1994 - 1997	10
M Sugiyama PhD	1992 - 1993	10
G Sutton PhD	1992 - 1995	10
S Tanaka PhD	1992 - 1993	10
S Thompson DPhil	1992 - 1992	10
P Wang PhD	1994 - 1997	10
D Wright	1993 - 1994	10
C K Yi PhD	1993 - 1996	10
Y Zhao PhD	1993 - 1994	10
J Zhong PhD	1994 - 1995	9

Appendix 3

Publications 1992 - 1993

(Abstracts, Contract Reports, etc., not included)

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Appendix 4: Curricula Vitae of Project Leaders

MARK J BAILEY B.Sc., M.Sc., Ph.D.

Project Leader: Microbial Ecology Group
(budget: CR £192k p.a.; SB £45k p.a.)

PERSONAL DETAILS:

Birthplace:	Ormskirk, England
Married:	Dr Amanda C. Bailey
Family:	Sophie

DEGREES:

Undergraduate:	Manchester Polytechnic	B.Sc. (Hons.)	1979, Biol. Sci.
Graduate:	University of Reading	M.Sc.	1980, Virology
Graduate:	University of Reading	Ph.D.	1983, Env. Virol.

PROFESSIONAL CAREER:

1989 - present	Group leader, SSO, NERC Institute of Virology & Environmental Microbiology
1987 - 1989	SSO, NERC Institute of Virology & Environmental Microbiology
1983 - 1987	Postdoctoral fellow, University of Birmingham
1980 - 1983	Research assistant, University of Reading

MEMBERSHIP OF PROFESSIONAL SOCIETIES:
Society for General Microbiology; American Society for Microbiology; American Phytopathology Society; International Society for Molecular Plant-Microbe Interactions (ISMPM).

PUBLICATIONS:

Todate:	35 papers, chapters (etc.) published, 8 *in press*.

EDITOR, EDITORIAL BOARDS:

1993	Editor *Bacillus thuringiensis*: An environmental biopesticide

Ph.D., D.Phil. THESIS EXAMINER:
UK; average 1 per year

POST-DOCTORAL AND GRADUATE STUDENTS (SINCE 1989):
8 Post-doctoral fellows, 8 pre-doctoral students (D.Phil., Ph.D.)

INVITED SEMINARS AND MEETINGS:
Universities and scientific meetings in the UK and EU countries as well as the USA; average *ca* 3 per year; co-organiser *Bacillus thuringiensis* 1991; organising committee for BAGECO4; organising committee for 7th ISMPM.

COMMITTEES (NATIONAL):
Working Group on monitoring GMMs (DOE/ACRE)
Member of HSE review committee
Chairman, OECD workshop on methods for monitoring microorganisms
Assessor: EECBiotech project proposals, Brussels

INVENTOR-INVENTIONS
Co-inventor and licensee of diagnostic kit for the detection of syphilis.

DAVID H L BISHOP M.A., D.Sc., F.I.Biol.

Director, NERC Institute of Virology & Environmental Microbiology
(105 staff, students, visitors; total budget £2.3m p.a.)

Project Leader: Molecular Virology Group
(budget: CR £174k p.a.; SB £81k p.a.)

PERSONAL DETAILS:

Birthplace:	London, England
Married:	Prof. Polly Roy (Univ. Alabama in B'ham; Oxford University)
Family:	Caren B.A., Andrew M.Eng., Alexander B.Sc.

DEGREES:

Undergraduate:	University of Liverpool	B.Sc. (Hons.) 1959, Biochemistry
Graduate:	University of Liverpool	Ph.D. 1962, Biochemistry
Graduate:	University of Oxford	M.A. 1984
Graduate:	University of Oxford	D.Sc. 1988

PROFESSIONAL CAREER:

1984-present	Visiting Professor of Virology, Oxford University Director, NERC Institute of Virology & Environmental Microbiology
1984-present	Fellow, St. Cross College, Oxford
1983-1984	Chairman, Department of Microbiology, Medical Center, University of Alabama at Birmingham, (UAB), USA
1981-1982	Visiting Fellow, Lincoln College and Sir William Dunn School of Pathology, Oxford
1977-1984	Senior Scientist, Diabetes Research Center, UAB
1975-1984	Senior Scientist, Comparative Cancer Center, UAB
1975-1984	Professor, Department of Microbiology, UAB
1975	Professor, Rutgers University, Waksman Institute of Microbiology, USA
1971 -1975	Associate Professor, Rutgers University
1970-1971	Associate Professor, Columbia University, USA
1969-1970	Assistant Professor, Columbia University, USA
1966-1969	Research Associate, University of Illinois, USA
1963-1966	Research Associate, University of Edinburgh, Scotland
1962-1963	Postdoctoral Fellow, C.N.R.S. GifsurYvette, France

AWARDS AND HONOURS:

1981	Nathanial A. Young Award in Virology
1988-present	Member, European Molecular Biology Organisation
1989-present	Fellow of the Institute of Biology
1994-present	Fellow of the Indian Virological Society

MEMBERSHIP OF PROFESSIONAL AND OTHER SOCIETIES:
EMBO; American Society for Virology; Society for General Microbiology; American Society for Microbiology; American Association for the Advancement of Science; Institute of Biology; Athenaeum Club.

PUBLICATIONS:

To-date: 290 papers, chapters (etc.) published, 6 *in press*.

EDITOR, EDITORIAL BOARDS:

1974-1982	Editorial Board	Journal of Virology
1975	Editor	Fundamental Aspects of Neoplasia
1978	Editor	Rhabdoviruses (3 volumes)
1979-1984	Associate Editor	Virology
1981	Editor	Repl. Negative Strand Viruses
1982-1989	Advisory Board	Archives of Virology
1983-1989	Editorial Board	Virus Research
1983	Editor	Doublestranded RNA Viruses
1984	Editor	Negative Strand Viruses (2 Vols)
1984-1989	Editorial Board	Journal of General Virology
1989-present	Editor	Virus Research
1993	Editor	Opportunities for molecular biology in crop protection
1994	Editor	Baculoviruses as expression vectors

Ph.D, D.Phil. THESIS EXAMINER:

USA, UK, France: numerous; average 3 per year

POSTDOCTORAL AND GRADUATE STUDENTS (SINCE 1971):

42 Postdoctoral fellows; 26 predoctoral students (Ph.D, D.Phil.).

INVITED SEMINARS AND MEETINGS:

Numerous; Universities and other research organisations throughout the UK and EU countries and elsewhere including: Algeria, Argentina, Austria, Australia, Brazil, Canada, China, Egypt, Finland, India, Israel, Japan, New Zealand, Republic of South Africa, Senegal, Slovak Republic, Sweden, Switzerland, USA, and the former USSR (and CIS); average *ca* 5 per year.

COMMITTEES (NATIONAL):

Since 1984: Numerous; NERC, MRC, SERC, MOD, Univ. Oxford, DTI, etc.

COMMITTEES (INTERNATIONAL):

1975-1979	National Cancer Institute Scientific Review Committee A;
1976-1981	Rhabdovirus Study Group, International Committee for Taxonomy of Viruses (ICTV);
1978-1987	Chairman, Bunyaviridae Study Group, ICTV;
1981-1986	WHO Study group on Rift Valley fever;
1982-1987	Chairman, Arenaviridae Study Group, ICTV;
1982-1984	Secretary and Treasurer, American Society for Virology;
1982-1987	Executive Committee Member, American Committee on Arthropod-Borne Viruses;
1982-1987	ViceChairman, Vertebrate Virus Subcommittee, ICTV;
1987-present	Member, Executive Committee of ICTV;
1987-1993	Chairman, Vertebrate Virus Subcommittee, ICTV;
1984-1993	Programme Committee, 6th9th Congresses of Virology;
1994-present	International Advisory Committee, 10th Congress Virology;
1990	Chairman Review Board: Laboratoire de Genetique des virus, CNRS;

1993-present Advisory Board, International Union of Microbiology Societies;
1993-present Vice-President, ICTV.

INVENTOR-INVENTIONS-PATENTS:
Co-inventor of multiple gene expression vector patents awarded in: Australia, Austria, Belgium, France, Greece, Germany, Italy, Luxembourg, Netherlands, Republic of South Africa, Spain, Sweden, Switzerland, United Kingdom; pending in USA, Canada and Japan; co-inventor patent application on AcNPV genome.

DESIGNATED SCIENTIST IN LICENCES AND MEMORANDA OF UNDERSTANDING:
Companies include Clontech, Commonwealth Serum Laboratories, Ingenasa, Oravax, PharMingen, Virbac, Wellcome; other organisations include: Australian Animal Health Laboratories, Onderstepoort Veterinary Research Institute, Texas A. & M. Universities Systems.

TIMOTHY F BOOTH B.Sc., Ph.D.

Project Leader: Virus Ultrastructure Group
(budget: CR £2k p.a.; SB £20k p.a.)

PERSONAL DETAILS:

Birthplace:	Berkeley, CA, USA
Married:	Dr S. Thompson (Oxford University)
Family:	Samuel, Megan

DEGREES:

Undergraduate:	University of Bath	B.Sc. (Hons.)	1981, App. Biol.
Graduate:	Thames Polytechnic	Ph.D.	1985, Biology

PROFESSIONAL CAREER:

1992 present	Group leader, SSO, NERC Institute of Virology & Environmental Microbiology
1987-1992	SSO, NERC Institute of Virology & Environmental Microbiology
1985-1987	Postdoctoral fellow, University of British Columbia, Canada

MEMBERSHIP OF PROFESSIONAL SOCIETIES:
Society for General Microbiology; American Society for Virology

PUBLICATIONS:

To-date:	28 papers, chapters (etc.) published, 2 *in press*.

POSTDOCTORAL AND GRADUATE STUDENTS (SINCE 1989):
2 pre-doctoral students (D.Phil.)

INVITED SEMINARS AND MEETINGS:
Universities and scientific meetings in EU countries; USA; average *ca* 3 per year;

AWARDS

1990	EMBO short-term fellowship

J IAN COOPER M.A., Ph.D.

Project Leader: Plant Virology Group
(budget: CR £59k p.a.; SB £115k p.a.)

PERSONAL DETAILS:

Birthplace:	Tynemouth, England
Married:	Audrey C. Cooper
Family:	Wendy, Elaine

DEGREES:

Undergraduate:	Durham University	B.Sc. (Hons.)	1965, Botany
Graduate:	University of London	M.Sc.	1966, Botany
Graduate:	University of St Andrews	Ph.D.	1972, Botany
Graduate:	University of Oxford	M.A.	1976

PROFESSIONAL CAREER:

1993-1994	Visiting fellow, University of Western Australia (on sabbatical leave)
1975-present	Group leader, UG7, NERC Institute of Virology & Environmental Microbiology
1972-1975	SSO, NERC Institute of Virology & Environmental Microbiology
1966-1972	Postdoctoral fellow, Scottish Horticultural (Crop) Research Institute

MEMBERSHIP OF PROFESSIONAL SOCIETIES:
Society for General Microbiology; Association of Applied Biologists

PUBLICATIONS:

To-date:	60 papers, books, chapters (etc.) published, 2 in press.

Ph.D., D.Phil. THESIS EXAMINER:
UK; average 1 per year

POST-DOCTORAL AND GRADUATE STUDENTS (SINCE 1989):
6 Post-doctoral fellows, 9 pre-doctoral students (M.Sc., D.Phil., Ph.D.)

INVITED SEMINARS AND MEETINGS:
Universities and scientific meetings in EU countries as well as elsewhere including Austria, Australia, Estonia, Canada, China, Finland, Hungary, Poland, Sweden and the USA; average *ca* 2 per year

JENNIFER S CORY B.Sc., D.Phil.

Project Leader: Virus Ecology and Biocontrol Group
(budget: CR £21k p.a.; SB £119k p.a.)

PERSONAL DETAILS:
Birthplace: London, England

DEGREES:

Undergraduate:	University of Sheffield	B.Sc. (Hons.)	1979, Zoology
Graduate:	University of Oxford	D.Phil.	1984, Entomol.

PROFESSIONAL CAREER:

1991 present	Group leader, SSO, NERC Institute of Virology & Environmental Microbiology
1984 1991	HSO, SSO NERC Institute of Virology & Environmental Microbiology

MEMBERSHIP OF PROFESSIONAL SOCIETIES:
Society for General Microbiology; Society for Invertebrate Pathology; British Ecological Society; Royal Entomological Society; Association of Applied Biologists; Society for Vector Ecology.

PUBLICATIONS:
To-date: 36 papers, chapters (etc.) published, 3 *in press*.

EDITOR, EDITORIAL BOARDS:
1993 Editor *Bacillus thuringiensis*: An environmental biopesticide.

Ph.D., D.Phil. THESIS EXAMINER:
UK; average 1 per year

POST-DOCTORAL AND GRADUATE STUDENTS (SINCE 1991):
4 Post-doctoral fellows, 6 pre-doctoral students (D.Phil., Ph.D.)

INVITED SEMINARS AND MEETINGS:
Universities, other research organisations and scientific meetings in the UK and EU countries as well as elsewhere including Brazil, Canada, Nicaragua and the USA; average *ca* 4 per year co-organiser *Bacillus thuringiensis* 1991:

COMMITTEES (NATIONAL):
Working Group on monitoring GMMs (DOE/ACRE)

ERNEST A GOULD B.Sc., Ph.D.

Assistant Director, NERC Institute of Virology & Environmental Microbiology

Project Leader: Flavivirus Group
(budget: CR £92k p.a.; SB £82k p.a.)

PERSONAL DETAILS:

Birthplace:	Redditch, England
Married:	Suzanne M. Gould
Family:	Kathryn, Richard, Jonathan

DEGREES:

Undergraduate:	University of Liverpool	B.Sc. (Hons.)	1965, Microbiol.
Graduate:	University of Liverpool	Ph.D.	1968, Virology

PROFESSIONAL CAREER:

1988-present	Assistant Director, UG6, NERC Institute of Virology & Environmental Microbiology
1991	Acting Director, NERC Institute of Virology & Environmental Microbiology
1979-1988	Senior Lecturer, London University School of Hygiene and Tropical Medicine
1979-1991	Visiting Professor, University Al Fateh
1970-1979	Lecturer, The Queen's University, Belfast
1968-1970	Research Fellow, Birmingham University

MEMBERSHIP OF PROFESSIONAL SOCIETIES:
Society for General Microbiology; American Society for Virology

PUBLICATIONS:

To-date:	75 papers, chapters (etc.) published, 5 *in press*.

EDITOR, EDITORIAL BOARDS:

1990-present	Editorial Board	Journal of General Virology
1990-present	Editorial Board	Virus Research
1994	Editor	Epidemiology and Infection

Ph.D., D.Phil. THESIS EXAMINER:
UK, Eire, Australia, Malaysia, India; average 34 per year

POSTDOCTORAL AND GRADUATE STUDENTS (SINCE 1970):
20 Postdoctoral fellows and predoctoral students (M.Phil., M.Sc., D.Phil, Ph.D)

INVITED SEMINARS AND MEETINGS:
Numerous; Universities and other research organisations in the UK and EU countries; average *ca* 3 per year.

COMMITTEES (NATIONAL):
Member of HSE Advisory Committee for Dangerous Pathogens
Member of Oxford University Bioresources Committee

IAN M JONES B.Sc., Ph.D.

Project Leader: Virus Protein Functions Group
(budget: CR £140k p.a.; SB £51k p.a.)

PERSONAL DETAILS:

Birthplace:	Llangollen, Wales
Married:	Harjinder K. Jones
Family:	Kiran, Marc

DEGREES:

Undergraduate:	University of Warwick	B.Sc. (Hons.)	1977, Biol. Sci.
Graduate:	University of Reading	Ph.D.	1980, Virology

PROFESSIONAL CAREER:

1987-present	Group leader, UG7, NERC Institute of Virology & Environmental Microbiology
1982-1987	Postdoctoral fellow, Sir William Dunn School of Pathology, University of Oxford
1980-1982	EMBO Fellow, Institut Jacques Monod, Paris

MEMBERSHIP OF PROFESSIONAL SOCIETIES:
Society for General Microbiology; American Society for Microbiology; American Phytopathology Society; International Society for Molecular PlantMicrobe Interactions (ISMPM).

PUBLICATIONS:

Todate:	49 papers, chapters (etc.) published; 4 *in press*.

EDITOR, EDITORIAL BOARDS:

1993-present	Journal of General Virology

Ph.D., D.Phil. THESIS EXAMINER:
UK, Australia; average 2 per year

POST-DOCTORAL AND GRADUATE STUDENTS (SINCE 1989):
11 Post-doctoral fellows, 5 pre-doctoral students (D.Phil., Ph.D.)

INVITED SEMINARS AND MEETINGS:
Universities and scientific meetings in the UK and EU countries; average *ca* 3 per year.

COMMITTEES (NATIONAL):
Virus Group, Society for General Microbiology (1994-1996)

INVENTOR INVENTIONS
Co-inventor patent on Factor IX protein.

PATRICIA A NUTTALL B.Sc., Ph.D.

Project Leader: Tickborne Pathogens Group
(budget: CR £99k p.a.; SB £110k p.a.)

PERSONAL DETAILS:

Birthplace:	Sheffield, England
Married:	R.W. Cragg C.Eng., M.I.Mech. E., M.B.I.M.
Family:	Amanda, Sophie

DEGREES:

Undergraduate:	University of Bristol	B.Sc. (Hons.)	1974, Microbiology
Graduate:	University of Reading	Ph.D.	1978, Virology

PROFESSIONAL CAREER:

1994-present	Group leader, IMP UG6, NERC Institute of Virology & Environmental Microbiology
1993	Visiting scientist, CSIRO Indooroopilly, Australia (on sabbatical leave)
1988-1994	Group leader, UG7, NERC Institute of Virology & Environmental Microbiology
1984-1988	Group leader, SSO, NERC Institute of Virology & Environmental Microbiology
1980-1984	HSO, NERC Institute of Virology & Environmental Microbiology
1977-1980	Postdoctoral fellow, Edward Grey Institute of Field Ornithology, Dept. Zoology, University of Oxford.

AWARDS AND HONORS:

1974-1977	Animal Health Trust Scholarship
1977-1980	Junior Research Fellowship, Wolfson College, Oxford
1990-present	Senior Research Fellowship, Wolfson College, Oxford

MEMBERSHIP OF PROFESSIONAL AND OTHER SOCIETIES:
American Society for Tropical Medicine & Hygiene; Royal Society of Tropical Medicine & Hygiene; Society for General Microbiology; European Association of Acarologists; British Society of Parasitology; Seabird Group; Morgan Sports Car and Morgan Three Wheeler Clubs.

PUBLICATIONS:

To-date:	101 papers, chapters (etc.) published, 8 *in press*.

EDITOR, EDITORIAL BOARDS:

1990-present	Editorial Board	Folia Parasitologia
1993-present	Editorial Board	Transactions of the Royal Society of Tropical Medicine & Hygiene
1993-present	Editorial Board	Acta Virologica

Ph.D, D.Phil. THESIS EXAMINER:
UK, Switzerland: average 23 per year

POST-DOCTORAL AND GRADUATE STUDENTS (SINCE 1984):
8 Post-doctoral fellows; 11 pre-doctoral students (Ph.D, D.Phil.)

INVITED SEMINARS AND MEETINGS:
Numerous; Universities and research institutions in the UK and EU countries as well as elsewhere including: Austria, Australia, Croatia, Czech Republic, Russia, Slovakia, Switzerland and the USA: average: *ca* 5 per year.

COMMITTEES (NATIONAL):

1983:	Society for General Microbiology, Convenor "Viruses of Birds", University of Warwick
1992-1995	NERC Special Topic in Wildlife Diseases

COMMITTEES (INTERNATIONAL):

1988, 1990, 1992, 1994	Convenor, European Tick Study Group, Oxford UK;
1989	Coorganiser, Second International Symposium on Arboviruses in the Mediterranean Countries, Dubrovnik Yugoslavia;
1992	Programme Committee, Fifth International Conference on Lyme Borreliosis, Arlington, USA;
1990-present	Bunyaviridae Study Group, International Committee for Taxonomy of Viruses (ICTV).
1993-present	Orthomyxoviridae Study Group, International Committee for Taxonomy of Viruses (ICTV).

INVENTOR-INVENTIONS-PATENTS:
Co-inventor on metazoan vaccines patent.

ROBERT D POSSEE B.Sc., Ph.D.

Project Leader: Molecular Biology of Baculoviruses Group
(budget: CR £142k p.a.; SB £66k p.a.)

PERSONAL DETAILS:

Birthplace:	Canterbury, England
Married:	Dr Linda A. King (Oxford Brookes University)
Family:	Simon, Daniel

DEGREES:

Undergraduate:	University of Birmingham	B.Sc. (Hons.)	1978, Biol. Sci.
Graduate:	University of Warwick	Ph.D.	1982, Virology

PROFESSIONAL CAREER:

1994	Visiting fellow, Dept. Genetics, University of Georgia, Athens, GA, USA (on sabbatical leave)
1990-present	Group leader, UG7, NERC Institute of Virology & Environmental Microbiology
1984-1990	Group leader, HSO, SSO, NERC Institute of Virology & Environmental Microbiology
1981-1984	Postdoctoral fellow, HSO, NERC Institute of Virology & Environmental Microbiology

MEMBERSHIP OF PROFESSIONAL SOCIETIES:
Society for General Microbiology; American Society for Microbiology; American Society for Virology; Biochemical Society; Society for Invertebrate Pathology.

PUBLICATIONS:
To-date: 71 papers, chapters (etc.) published.

EDITOR, EDITORIAL BOARDS:

1988-present	Virology
1989-1992	Journal of general virology

Ph.D., D.Phil. THESIS EXAMINER:
UK; average 1 per year

POST-DOCTORAL AND GRADUATE STUDENTS (SINCE 1989):
8 Post-doctoral fellows, 8 pre-doctoral students (D.Phil., Ph.D.)

INVITED SEMINARS AND MEETINGS:
Universities; other research organisations and scientific meetings in the UK and EU countries as well as elsewhere including Argentina, Switzerland, and the USA; average *ca* 5 per year.

COMMITTEES (NATIONAL):

1990-present	Baculoviridae Study Group, International Committee for Taxonomy of Viruses

INVENTOR-INVENTIONS-PATENTS
Co-inventor for genetically engineered baculovirus insecticides patent; co-inventor patent patent application on AcNPV genome.

POLLY ROY M.Sc., Ph.D.

Project Leader: Orbivirus Group
(budget: CR £452k p.a.)

PERSONAL DETAILS:

Birthplace:	Calcutta, India
Married:	Prof. D.H.L. Bishop
Family:	Alexander B.Sc.

DEGREES:

Undergraduate:	University of Calcutta	B.Sc. (Hons.)	1961, Botany
Graduate:	University of Calcutta	M.Sc.	1964, Biochem.
Graduate:	New York University	Ph.D.	1971, Virology

PROFESSIONAL CAREER:

1990-present	Senior Research Scientist, Laboratory of Molecular Biophysics, University of Oxford
1985-1990	Senior Scientist, Dept. Plant Sciences, Oxford University and NERC Institute of Virology & Environmental Microbiology
1985-present	Professor, Dept. International Health Science, UAB, USA
1984	Visiting Scientist, Sir William Dunn School of Pathology, Oxford Univ
1981-1985	Associate Professor, Department of Environmental Health, UAB, USA
1977-1981	Assistant Professor, Department of Environmental Health, UAB, USA
1975-1977	Research Fellow, Department of Microbiology, UAB, USA
1971-1975	Research Associate, Waksman Institute of Microbiology, Rutgers University, USA

AWARDS AND HONORS:

1959-1963	D.P.I. Scholar (India)
1964-1966	PL480 Fellow (India)
1972	Founders Day Award, New York University
1991	Fellow of the Indian Virological Society

MEMBERSHIP OF PROFESSIONAL AND OTHER SOCIETIES:
American Society for Virology; Society for General Microbiology; American Society for Microbiology; Sigma Xi; American Association for the Advancement of Science; European Society for Veterinary Science; New York Academy of Science; American Society of Tropical Medicine and Hygiene.

PUBLICATIONS:

To-date:	160 papers, chapters (etc.) published, 12 in press.

EDITOR, EDITORIAL BOARDS:

1994-present	Editorial Board	Journal of General Virology
1993-present	Editorial Board	Indian Journal of Virology
1986	Co-editor	Orbiviruses and Birnaviruses
1978	Co-editor	Current Topics in Microbiology

Ph.D. THESIS EXAMINER:
USA: average 1-2 per year

POSTDOCTORAL AND GRADUATE STUDENTS (SINCE 1971):
51 Postdoctoral fellows; 20 predoctoral students (Ph.D, D.Phil.)

INVITED SEMINARS AND MEETINGS:
Numerous; Universities and other research organizations throughout the EU countries and elsewhere including: Canada, China, India, Japan, Republic of South Africa, Switzerland, USA, and the former USSR (and CIS); average: *ca* 5 per year.

COMMITTEES (INATIONAL):

1994-present	BBSRC Plant and Microbial Science Committee

COMMITTEES (INTERNATIONAL):

1991	OIE: Bluetongue Diagnostics and Vaccines
1992-1994	Co-ordinator: Biotechnology and Vaccine Delivery (EEC)

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