A RECOMBINANT DNA APPROACH TO RIFT VALLEY FEVER VIRUS VACCINES

Marc S. Collette
A F Purchio, K Keegan, M Parker, and J Dalrymple

Rift Valley fever virus (RVFV) is a member of the phlebovirus genus of the family Bunyaviridae. It is the etiologic agent of a serious disease in livestock and represents a significant potential threat to human health. Although Rift Valley fever and the causative virus appeared to be confined to sub-Saharan Africa, the massive epidemic in Egypt in 1977 indicated that this limited distribution may not be absolute. Considering the high containment requirements for work with RVFV, the reversion possibility of live-attenuated virus vaccines, and the expense in producing formalin-inactivated preparations, we have explored the feasibility of employing recombinant DNA technologies to generate microbially-produced subunit vaccines for protection against this disease.

The genome of RVFV consists of three RNA segments of negative polarity designated L, M, and S. It has been shown with other bunyaviruses that virus neutralizing determinants reside on the viral glycoproteins, and that the genetic information encoding these polypeptides is present on the M RNA. Assuming an analogous situation for RVFV, we have molecularly cloned complementary DNA copies of the RVFV M RNA. The entire M RNA segment of the RVFV genome is represented in four overlapping plasmid clones. That the entire M RNA segment is in fact represented was established by demonstrating that sequences present at the 3' and 5' extremities of the aligned cDNA clones were complementary to one another, a characteristic of the RNAs of members of the Bunyaviridae family. The complete nucleotide sequence corresponding to the entire M RNA has been determined. Within the 3884 nucleotides that made up the M segment, an open reading frame of 3621 nucleotides is present. By purifying and sequencing the amino termini of the two viral glycoproteins, G1 and G2, we were able to establish that: (i) these two polypeptides were indeed encoded by the M RNA segment of RVFV; (ii) the coding sequences of both proteins are present in the same major open reading frame in a non-overlapping manner, and (iii) their order along the major open reading frame with respect to the viral genomic RNA is 3'-G2-G1-5'. We have constructed plasmid expression vectors that allow for the synthesis in Escherichia coli of polypeptides encoded by select regions of the clones M DNA. Over 90% of the sequences encoding each of the mature glycoproteins G1 and G2 has been expressed in bacteria. These bacterially-produced RVFV glycoprotein analogues are being evaluated for their potential use in vaccine formulations. Our results indicate that the genetically-engineered RVFV glycoprotein analogues will be useful in future vaccine development.

HEALTH CARE SERVICES FOR DEVELOPING COUNTRIES

Dr. S.M.X. Corea

The paper presents information on the methods of identification of health problems in developing countrees, together with descriptions of the existing health care services and a discussion on the indices of health necessary for monitoring and evaluation of the health care system.

It commences with a review of the health problems over the past three decades, common to less developed countries ,with particular reference to the South East Asian region. Attention is also drawn to the fact that there is a changing pattern of morbidity and mortality which could be anticipated in the wake of large scale development programs which are being carried out.

The next section deals with some of the identifiable causes of the existing problems and attempts to categorize the possible solutions into short, medium and long terms.

The final section discusses the existing health care systems in the developing countries and their impact on the health of the population. Suggestions for improvement of the health care delivery have been made and the need for the establishment of an effective monitoring and evaluation system as an integral part of the health care service has been spotlighted.

RECENT ADVANCES IN SCHISTOSOME MAINTENANCE FOR LABORATORY STUDIES

Combes, Claude
J. Jourdane, L Razafiniary-Andriambololona and D. Imbert-Establet

Until recently, schistosomes were maintained in laboratory by classical methods, using alternatively a vector snail and a vertebrate ; the latter can be a rodent (white mouse or hamster) or a primate (rhesus monkey).

On the basis of the microsurgical method proposed by CHERNIN (1966), JOURDANE (1978) succeeded in cloning S. mansoni by transplanting sporocysts from a donor snail (infected with a single miracidium) to recipient snails. The transplantation can be repeated indefinitely, resulting in a clone (JOURDANE and THERON, 1980). From cercariae produced by a male clone and a female clone it is possible to return to the classical cycle at any moment to obtain adults. More than thirty successive transplantations have been realized in our laboratory without loosing infectivity. Similar results, with slightly different techniques, have been obtained with S. haematobium (JOURDANE, KECHEMIR and COMBES, 1981), S. japonicum (JOURDANE, LIANG and BRUCE, in press) and S. bovis (JOURDANE, MOUAHID and TOUASSEM, in press).

The method is useful not only because it greatly simplifies and reduces the cost of schistosome maintenance, but also because clones are absolutely genetically stable, as was proved by isoenzymatic studies (IMBERT-ESTABLET, ROLLINSON and ROSS, in press).

Regarding the definitive host (when adults are required), a small, 10 cm high, pro-simian (Microcebus murinus) from Madagascar has been demonstrated to be a excellent host for S. mansoni (RAZAFINIARY-ANDRIAMBOLOLONA, thesis in press) ; this lemurian, which can be bred in the laboratory (ANDRIANTSIFERANA, 1975) is well adapted for studies requiring a primate as a host for schistosomes and is easily kept and fed thanks to its very small size.

These advances can facilitate laboratory studies and reduce costs in schistosome research or antigen production.

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DIAGNOSIS OF GENITAL HSV INFECTIONS IN WESTERN INDUSTRIALIZED NATIONS

Lawrence Corey, M.D.

Diagnosis of Genital HSV Infections in western industrialized nations. L. COREY. University of Washington, Seattle, WA

Herpes Simplex Virus (HSV) is the commonest agent isolated from genital ulcerations, accounting for 20 - 50% of ulcerative lesions in the patients attending STD Clinics. Considerable overlap exists in the clinical manifestations of genital HSV within those of H. ducreyi and T. pallidum and other noninfectious causes of genital ulcerations. In addition dual HSV and T. pallidum or HSV and H. ducreyi infections may occur. As such, laboratory confirmation of the cause of a genital ulcer nearly always should be sought. The laboratory diagnosis of HSV infection relies on the cultivation of virus in tissue culture, detection of viral particles by electromicroscopy, detection of viral antigen by immunologic method or demonstration of cytopathological changes by Papanicolaou or Giemsa staining. The sensitivity of all laboratory assays for HSV varies with the stage and anatomic site of the lesion. HSV can be isolated in tissue culture from 94% of vesicular, 87% of pustular, 70% of ulcerative and 20% of crusted genital lesions. Studies using polyclonal antibodies and immunofluorescent methods have shown viral antigen in 75% of vesicular-pustular lesions, 50% of ulcerative lesions and 25% of crusted lesions. We have recently conducted a study comparing viral isolation with the detection of HSV antigen using monoclonal antibodies in an immunofluorescent assay in a population having a high prevalence of genital herpes. In this population the two assays were of nearly equal sensitivity in vesicular pustular and ulcerative lesions, however; the FA antigen detection method was only 50% as sensitive as viral isolation in detecting cervical HSV infection. Thus while there have been some inroads in the use of rapid diagnostic methods for genital HSV infections, more work needs to be done in developing sensitive rapid viral diagnostic techniques to evaluate the presence of HSV antigen in cervical and/or urethral secretions.

SELVATIC YELLOW FEVER AND DENGUE IN WEST AFRICA

Michel Cornet Roger Jean Paul
M. Germain, J. F. Saluzzo, R. Cordellier, J. C. Roche, J. P. Hervy, Max
M. Lhuillier, J. P. Herve and J. P. Digoutte
Jean Paul

Yellow fever is always a major public health problem in West Africa, where several epidemics occured during the past 20 years. Intensive surveys in presumed selvatic areas furnished important serological data and a lot of virus isolations from wild mosquitoes and monkeys; the main vectors involved are Aedes furcifer, Ae.taylori, Ae.luteocephalus, Ae.africanus and Ae.opok. These informations brought to a new definition of epidemiological zones. Among these the 'emergence' zone covers humid and semi-humid savannahs, and is the site of intense epizootic circulation of the virus. Transovarial transmission in mosquitoes and perhaps in ticks might explain the maintenance of the virus through the dry season, so that the arthropods might be considered as vectors and reservoirs as well; however long term maintenance of the virus probably needs horizontal transmission between vectors and monkeys. Another important feature is the apparent mildness of human infections in selvatic areas.

Dengue viruses are a quite recent discovery in West Africa. Human cases of dengue 1 are known to occur in Nigeria and Senegal, while dengue 2 seems to be more widespread. Selvatic circulation of these viruses occurs in Nigeria for both types, in Upper-Volta, Ivory-Coast, Guinea and Senegal for dengue 2. The transmission cycles seem very close to those of yellow fever virus, involving the same vectors and the same vertebrate hosts, but the dynamics of the epizootics are different. Transovarial transmission of dengue 2 virus in mosquitoes is highly suspected, since 2 virus strains were isolated from wild caught males. Human infections are mild, as far as known, and no haemorrhagic or schock syndroms were noticed in West Africa.

TREATMENT OF FALCIPARUM MALARIA WITH HALOFANTRINE

J. P. Coulaud
A. G. Saimot, J. F. Rossignol

Drug resistance of Plasmodium falciparum strains has now spread to East Africa and Madagascar. The 4-amino-quinolines are not the only drugs concerned, since strains in South East Asia are resistant to quinine and methanol quinolines such as mefloquine. Other drugs are being developed, notably halofantrine which belongs to the phenantren-methanol group.

40 patients with acute falciparum malaria were treated in the tropical diseases wards of Claude Bernard' Hospital in Paris. These patients contracted malaria in South East Asia, Africa or Madagascar. 18 were given a total dose of 1000 mg halofantrine (500 mg on arrival and 500 mg six hours later). 22 were given 1500 mg in three doses of 500 mg at intervals of 8 hours. The drug was well tolerated : 2 cases of nausea, 1 case of delayed skin rash with pruritus. 17 of the 18 patients treated with 1000 mg and the 22 patients treated with 1500 mg had a negative blood smear on Day 4. Four cases of recrudescence were observed between Day 17 and Day 21 ; this is consistent with pharmacokinetics of the drug. No case of in vitro resistance to halofantrine was observed.

G. PICHON

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