The arenaviruses: some priorities for future research

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In this paper Lassa virus is used as a model in pinpointing priorities for future research on the arenaviruses. Suggestions for specific investigations and public health measures cover the detection of Lassa virus infection, the pathology and therapy of the disease, and its prevention and control.

Although the first arenavirus was discovered more than 40 years ago, the recognition of a family of agents containing ribonucleic acid and having common morphological properties dates only from 1969. With a single exception, these viruses are primarily parasites of specific rodents and appear to survive by both horizontal and vertical transmission without the need for intermediate hosts, such as arthropod vectors or other vertebrates.

Four of these agents are pathogenic for man, and three of them—Lassa, Junin, and Machupo viruses—produce severe disease with significant mortality. Lassa virus, the most recently recognized, is also the most widely distributed and appears to have the greatest potential for direct spread from person to person. For these reasons, I propose to use it as a model for pinpointing needs and making suggestions for specific investigations and public health measures; but I want to emphasize that many of these points apply equally or in modified form to the haemorrhagic fevers caused by Junin and Machupo viruses. No attempt will be made to present an exhaustive survey of present knowledge or to assess future priorities. Earlier speakers have made excellent appraisals of arenavirus biology, of the pathophysiology of infection in vertebrates, and of the taxonomy and ecology of Mastomys and other implicated rodents. Furthermore, the varied national and international views of the importance of Lassa fever in relation to other pressing public health problems inevitably dictate that individual health workers and concerned governments will have their own distinct sets of priorities.

DETECTION OF LASSA VIRUS INFECTION

The essential requirements are clinical awareness of the disease, laboratories in which the virus can safely be studied, appropriately trained laboratory personnel, sensitive diagnostic techniques, and standardized, safe reagents for their execution. This symposium has starkly revealed the urgent need to develop all these diagnostic resources.

Although WHO has published and disseminated a summary of the salient clinical and epidemiological features of Lassa fever, awareness of the disease is far from adequate, particularly in Africa, where cases are most likely to occur. Basic information certainly ought to be included in the curricula of every medical school south of the Sahara. Others more familiar than I with teaching practices and resources in this region must offer counsel as to how this can be best achieved.

There is a painful shortage of specialized laboratories that can safely undertake intensive work on virulent Lassa and South American arenaviruses. At present only the Atlanta facility at the Center for Disease Control (CDC) is functional. The only other North American laboratory that would be capable of such work is the US Army Medical Research Institute for Infectious Diseases located in Frederick, Maryland. Conversations with other symposium participants have revealed that similar laboratories are under construction in the UK and the Federal Republic of Germany. At least one such facility ought to be developed in Africa, wherever national resources and priorities permit. The specific training of already experienced virological personnel to work in these special laboratories should be easy to arrange.

The only methods currently in use for identification of Lassa virus and antibodies to it are comple-
ment fixation and immunofluorescence. Although useful, both methods have major limitations in terms of specificity (there may be more than one immunotype of Lassa virus) and sensitivity. A virus-specific neutralization test or its equivalent is urgently needed in order to determine whether all Lassa strains are similar and to make more efficient estimates of population-based immunity status in different countries. The indirect haemagglutination test for Machupo virus described by Gajdamović offers one possible approach. Radioimmunoassay techniques employing purified virions or envelope antigens and anti-Lassa immunoglobulins may afford another.

Finally, for the immediate future, inactivated antigens and appropriate reference sera must be provided to laboratories wishing to diagnose Lassa virus infection and search for antibodies in sera, especially of human origin. The CDC has done this on a limited scale and will endeavour to respond to all reasonable requests for these materials.

PATHOPHYSIOLOGY AND THERAPY OF LASSA FEVER

Nathanson has presented a remarkable synopsis of current understanding of arenavirus-caused disease and emphasized the opportunities for learning more through the use of animal models. Answers to several questions, however, need to be obtained directly by studies in man. Can we obtain from patient cells that nearly always contain virus-specific antigens? If so, rapid, relatively safe diagnoses can be made early in the course of disease. The search might include pharyngeal scrapings, urinary sediments, blood leukocytes, bone marrow aspirates, or skin biopsies. What causes the shock syndrome so conspicuous in Lassa fever and South American haemorrhagic fever? Do these arenaviruses significantly depress host immune function, leading to severe secondary microbial infection? Is virus-specific passive antibody of real therapeutic value in arenavirus disease? Uncontrolled clinical experience suggests that it may be and the report by Eddy et al. establishes that lethal Machupo virus infection in the rhesus monkey affords a positive model. Many of the answers to these and other questions probably require intensive study of occasional patients cared for in highly specialized centres; others can be obtained by disciplined, if simple, observations of more cases in areas where the viruses are endemic.

PREVENTION AND CONTROL OF LASSA FEVER

Bolivian haemorrhagic fever has been effectively curtailed by reduction of peridomestic populations of the reservoir-vector rodent Calomys callosus. Attenuation of Junin virus provides significant hope that Argentine haemorrhagic fever may one day be prevented by vaccination. These successes afford broad guidelines for specific work on Lassa fever. Nevertheless, I suspect that definitive solutions to the problem of preventing this disease will prove more difficult. We need to know how many kinds of Mastomys rodent exist in Africa and whether all of them are capable of maintaining and transmitting Lassa virus. We must also determine the ecological interrelationships between Mastomys and the presumed non-reservoir genera Rattus and Mus. This knowledge might conceivably permit disease control by biological substitution of appropriate rodent species or subspecies. It might also demonstrate that simplistic "control" of rodent populations is contraindicated. Establishment of small breeding colonies of Mastomys in several African countries, especially those where Lassa fever has not yet been recognized, so that the dynamics of viral biology can be differentially assessed in maximum security laboratories, is one practical example of a worthwhile effort requiring international cooperation.

Attenuation of Lassa virus appears to be possible, as does the extraction and purification of immunizing antigens from the virion envelope. More work on the latter approach, and indeed on the basic molecular biology of arenaviruses, is indicated and it would be quite feasible to employ non-virulent agents, such as Tacaribe, Tamiami, or Amapari viruses, as initial models. Actual progress toward Lassa virus vaccines, however, will be slower, depending on the number of laboratories equipped to handle the agent with safety.

SOME FINAL PRIORITIES

Geographical definition of the natural distribution of Lassa fever is essential. Assuming that a good technique for detection of persistent antiviral antibodies soon becomes available, we must decide how best to use it. Since there is likely to be discontinuous, focal localization of the virus, initial serum surveys should comprise samples from adults representing as many villages and individual dwellings as possible, rather than complete family-based surveys from fewer communities. Since Lassa fever is asso-
ciated with a high rate of abortion and since persons caring for patients who abort have an excessive risk of acquiring infection, the ideal approach might be to test persons routinely engaged in midwifery, whether or not they are medically trained. This concept should first be tested in Nigeria and Sierra Leone, where the disease is known to be endemic.

Facilities for the isolation and care of Lassa fever patients, both in Africa and elsewhere, must be improved. This is perhaps the most self-evident need to emerge from the symposium. Meeting this need is largely an individual national responsibility, but one that should be faced directly by health officials of each concerned government.

The same advice must be given to governments outside Africa with respect to the problem of "importation" of Lassa fever from endemic areas. An acutely ill person, anywhere on earth, will return to his home country and family if he possibly can. An internationally sponsored ban on the travel of patients with Lassa fever would not completely solve the matter. In the end, public health policies will need to be formulated to care for individuals and to prevent secondary infections at home.

As mentioned above, the use of convalescent human plasma or immunoglobulin may well represent an important therapeutic weapon in acute arenavirus-caused disease. But these agents must actually be obtained and banked and must have known antibody titres. International cooperation is clearly vital to the success of such a programme, especially in identifying potential donors, determining antibody titres, maintaining inventory information on plasma, arranging for the preparation of immunoglobulin, and collecting data on the efficacy of these materials in disease treatment.

RÉSUMÉ

LES ARÉNAVIRUS: QUELQUES ASPECTS PRIORITAIRES POUR LES RECHERCHES FUTURES

Sur les dix arénavirus actuellement reconnus, quatre provoquent des maladies aiguës chez l’homme. L’infection par trois de ces virus — Junin, Machupo et Lassa — peut provoquer des états morbides graves et la mort. Ces trois agents sont des parasites naturels de certains rongeurs sauvages bien déterminés. En raison de son plus grand potentiel de transmission directe chez l’homme et en raison de sa distribution géographique plus large, le virus de Lassa constitue, parmi les arénavirus, le problème de santé publique le plus important tant en Afrique qu’en dehors de ce continent.

Le manque d’installations de laboratoire pour travailler sur le virus de Lassa dans de bonnes conditions de sécurité a freiné les progrès de la connaissance de la biologie de ce micro-organisme. La nécessité de développer ces installations a été la priorité la plus fréquemment évoquée pendant ce symposium. Il est urgent également de mettre au point de techniques spécifiques et sensibles pour la détection du virus de Lassa et des anticorps correspondants chez l’homme et chez les rongeurs. Par exemple, on n’est parvenu à mettre au point aucun système satisfaisant de neutralisation des virus jusqu’à présent; sans cette épreuve ou sans un équivalent biologique, il n’est pas possible d’établir une carte de la distribution naturelle du virus de Lassa ni de savoir s’il existe des types immunologiques distincts de virus.

Divers observation ont été présentées qui confirment la thèse selon laquelle l’administration d’anticorps passifs spécifiques des arénavirus peut être utile pour traiter et prévenir la maladie aiguë chez l’homme. La collecte et l’évaluation clinique définitive de plasma humain anti-Lassa a été considéré comme un projet important à mener à relativement court terme.

Enfin, il a été démontré que le réservoir animal du virus de Lassa — le rongeur Mastomys natalensis — est probablement une espèce complexe. Les formes à nombre chromosomique de 32, 34 et 38 ont été identifiées. Des études internationales collectives sont nécessaires pour déterminer la distribution géographique et écologique de ces différentes espèces de Mastomys; évaluer leur optitude relative à entretenir une infection chronique avec excrétion de virus de Lassa dans les urines; et mesurer les résultats écologiques de la compétition chez Mastomys et les autres rongeurs tels que Rattus et Mus.