DTIC
ELECTE
JAN 6 1983
A

Journal of Medical Virology 10:45–54 (1982)

AD A123093

Inbred Rat Strains Mimic the Disparate Human Response to Rift Valley Fever Virus Infection

C.J. Peters and T.W. Slone

Department of Viral Pathogenesis and Immunology, Virology Division (C.J.P.) and Pathology Division (T.W.S.), U.S. Army Medical Research Institute of Infectious Diseases, Fort Detrick, Frederick, Maryland

Rift Valley fever virus (RFFV) has long been a major pathogen of domestic animals and humans in sub-Saharan Africa. In the last 5 yr it has been recognized that this agent not only causes a self-limited febrile illness in humans but may also lead to fatal hemorrhagic fever and encephalitis. In 1977 the disease invaded Egypt for the first time in recorded history, resulting in an extensive epizootic/epidemic and threatening additional spread into the Middle East. Because of this unprecedented geographical extension and the florid human disease associated with it, we have studied the pathogenicity of an Egyptian isolate (Zagazig Hospital 501) for laboratory animals. During the course of these studies, inbred rat strains were found to have three distinct patterns of response. Wistar-Furth and Brown Norway rats were exquisitely susceptible to the virus and died with extensive hepatic necrosis 3 to 5 days after inoculation of only 5 plaque-forming units (pfu). Lewis, Buffalo, DA, and Fischer 344 rats resisted subcutaneous infection with 5×10^5 pfu. ACI and Maxx rats were moderately susceptible to the lethal effects of 5×10^3 to 5×10^5 pfu of the virus and died within 2 to 3 wk with encephalitis. These findings suggest that the genetic susceptibility of the host is responsible for the markedly different evolution of RVF in the rats. The clinical and virologic events following rat inoculation resembled the course of benign, encephalitic, or fulminant human disease. The inbred rat model may be useful in defining the critical determinants of severe human RVF and suggests that more attention should be directed to host genetic factors.

Key words: Rift Valley fever, inbred rats, animal model for human disease

INTRODUCTION

From its initial isolation in Kenya in 1931 until the 1970s, the etiologic agent of Rift Valley fever (RFFV) was regarded as an unclassified mosquito-borne virus causing epizootics in African domestic animals south of the Sahara [reviewed by Peters and

Accepted for publication March 20, 1982.

Dr. Slone is now at US Army Biomedical Laboratory, ATTN: SGRD-UV-VC (Slone), Aberdeen Proving Ground, MD 21010.

Address reprint requests to Dr. C.J. Peters, Deparment of Viral Pathogenesis, Virology Division, US Army Medical Research Institute of Infectious Diseases, Fort Detrick, Federick, MD 21701.

0146-6615/82/1001-0045 $03.00 © 1982 Alan R. Liss, Inc.

DTIC FILE COPY

83 01 06 077

Meegan, 1981]. Infection of man often occurred after contact with fomites or aerosols from infected animal carcasses but was thought to be invariably benign except for rare ocular complications. Over the last decade, our perceptions of RVF virus have changed markedly. Morphologic [Murphy et al, 1973], biochemical [Rice et al, 1980], and serologic [Shope et al, 1980] evidence has placed it within the Phlebovirus genus, Phlebotomus Fever serogroup, of the family Bunyaviridae [Bishop et al, 1980]. Virus isolation and vector competence studies have emphasized that mosquitoes may not be the sole arthropod vector in epizootics and indeed may not be the vector that maintains the virus in its sylvatic cycle. Severe and fatal cases of hemorrhagic fever or encephalitis associated with RVF were diagnosed in South Africa [Van Velden et al, 1977] and Zimbabwe [Maar et al, 1979; Swanepoel et al, 1979] in 1975. It is still not known whether these complications have occurred for years and only now are being recognized or whether they represent a change in the clinical spectrum of RVF. In any case, in 1977 a major RVF epidemic occurred in Egypt for the first time [Meegan and Shope, 1981]. The virus had a devastating effect in sheep and other domestic animals, caused more than 20,000 human illnesses, and resulted in at least 600 human fatalities [World Health Organization, 1979]. The Egyptian epidemic provided ample confirmation of the potential of RVF to be complicated by ocular abnormalities, encephalitis, or hemorrhagic fever [Abdel-Wahab et al, 1978; Imam et al, 1979; Laughlin et al, 1979; Siam et al, 1979]. These forms of the disease occurred in a minority of cases (perhaps 0.1 to 1% of the total), but their devastating effects in otherwise healthy persons have led to much speculation concerning their genesis.

In the course of laboratory studies of an Egyptian RVFV isolate we encountered an inbred rat model that mimics the spectrum of human disease and illustrates the extent to which the genetic constitution of a single host species may influence the outcome of RVFV infection.

MATERIALS AND METHODS

Virus and Assays

The Zagazig Hospital 501 strain of RVFV was isolated during the 1977 epidemic by Dr. James Meegan, NAMRU3, Cairo, Egypt, from a patient with fatal hemorrhagic fever hospitalized in the Zagazig Fever Hospital 83 km northeast of Cairo. Viremic human serum was passed twice in diploid fetal rhesus lung cells (DBS-103) in this laboratory before use. In selected experiments rats were infected with this virus and a viremic serum sample from Wistar-Furth or a 20% brain homogenate from moribund ACI rats used for further study. Virus was assayed by inoculating 1.6-cm diameter Vero cell monolayers with 50 μl of sample diluted in Hanks' balanced salt solution buffered to pH 7.3 with 20 mM HEPES and containing 2% heat-inactivated calf serum, 50 μg/ml streptomycin and 50 U/ml penicillin (HBSS/H/2%CS/PS). After 1 hr at 37°C a 0.5-ml overlay maintained at 43°C was applied (Eagle's basal medium with Earle's salts, HEPES buffer, 4% heated calf serum, 50 U/ml penicillin, 50 μg/ml streptomycin, and 0.5% agarose). Following 4 days incubation at 37°C in 5% CO_2, the same overlay containing 1:10,000 neutral red was added and plaques enumerated the following day. To determine virus neutralizing antibodies, four-fold serum dilutions from 1:10 to 1:160 in HBSS/H/2%CS/PS were mixed with an equal volume of diluted virus and incubated at 37°C for 1 hr. Residual infectivity was determined by inoculating Vero cell monolayers with 50 μl of suspension originally containing 30 to 100

pfu of virus and applying a neutral red overlay on day 3. The plaque-reduction neutralization titre (PRN_{80}) was the highest serum dilution reducing the input virus plaques tabulated on day 4 by 80% or more.

Animals and Inoculation

Unless otherwise noted all rats were purchased from Microbiological Associates, Walkersville, MD. DA rats were a gift of Dr. Previn Bhatt, Yale University, New Haven, and were bred in this laboratory for use. Comparative studies were performed on Fischer 344 rats from the Frederick Cancer Research Center, Frederick, MD and ACI rats from Laboratory Supply Co., Indianapolis, IN. Female rats 10 to 15 wk of age were used throughout. All injections and blood sampling were performed under ether anesthesia.

Virus dilutions were prepared in HBSS/H/2%CS/PS and inoculated subcutaneously (sc), intraperitoneally (ip), or intravenously (iv) in a volume of 0.1 ml or intracranially in a volume of 0.025 ml. Rats receiving 7.7 log pfu were given 1 ml undiluted virus stock. Animals were examined daily and survivors tabulated. At 28 to 25 days postinoculation rats were exsanguinated for antibody determination. Several rats that had recently died or that were in a moribund state were subjected to virologic and histopathologic examinations. Brain, liver, and serum were frozen at -70°C and the remainder of the animal fixed in buffered neutral formalin. Parrafin-embedded sections were examined after hematoxylin and eosin staining. Organs were thawed, triturated to a 10% suspension in HBSS/H/10%CS/PS with sand in a mortar and pestle, clarified at 2,000 rpm for 15 min, and decimal dilutions titrated in Vero cell monolayers. Blood or serum gave similar results in preliminary experiments and are used interchangeably.

RESULTS

Several inbred rat strains were inoculated sc with a moderate ($10^{3.7}$ pfu) or high ($10^{5.7}$ pfu) virus dose (Table I). Three different response patterns were observed: a)

TABLE I. Inbred Rat Strains Differ in Their Responses to RVF Infection

Rat Strain	AgB[a]	Virus dose[b]	Number rats alive on day 0	7	28	Percent mortality	Mean day of death
Wistar-Furth	2	5.7	5	0	0	100	3.0
		3.7	10	1	1	90	3.2
Brown Norway	3	5.7	2	0	0	100	2.5
		3.7	10	0	0	100	3.0
ACI	4	5.7	10	10	5	50	16.0
		3.7	10	9	9	10	15.0
Maxx	3	5.7	10	10	6	40	11.0
		3.7	10	10	5	50	13.8
Fischer 344	1	5.7	20	18	17	15	6.7
		3.7	14	14	13	7	15.0
Buffalo	6	5.7	10	10	9	10	10.0
		3.7	5	5	5	0	
DA	5	5.7	5	5	5	0	
		3.7	5	5	5	0	
Lewis	1	5.7	10	10	10	0	
		3.7	10	10	10	0	

[a]Major histocompatability complex haplotype [Gasser, 1977].
[b]Log $_{10}$ number of pfu of Zagazig Hospital 501 strain of RVF virus inoculated sc.

Wistar-Furth and Brown Norway rats died within 4 days of inoculation. They appeared well until a few hours before death, when they assumed a hunched posture with ruffed fur and weakness. b) ACI and Maxx rats were intermediate in susceptibility, with only 10 to 50% dying. Those rats that succumbed did so predominantly in the second or third week of illness with clinical signs of central nervous system damage, often reflected in an ascending paralysis. c) Lewis, Fischer 344, DA, and Buffalo rats were largely resistant to the lethal effects of RVF inoculation. They presumably were infected, since they developed PRN_{80} titers of 1:160 or greater in serum samples obtained 28 to 35 days postinoculation. The above studies were repeated in Fischer 344 and ACI rats from alternate sources (Frederick Cancer Research Center, and Laboratory Supply Co., respectively) with similar results. There was no relation to the major histocompatibility type (AgB) [Gasser, 1977].

Histopathologic examination of moribund animals (Table II) indicated that the early deaths were due to severe hepatic necrosis. Livers were characterized by severe diffuse hepatocellular necrosis with small numbers of Councilman-like bodies, scant neutrophilic infiltrate, and congestion of variable severity (Fig. 1). Less severe lesions were consistently noted in several other organs. Large numbers of neutrophils, most of them karyorrhectic, were located throughout the red pulp of the spleen. A few neutrophils, some karyorrhectic, were present in most glomerular tufts of the kidneys. There was mild lymphoid depletion with occasional minimal necrosis of periarteriolar lymphatic sheaths in the white pulp of the spleen and mild lymphoid necrosis of the thymic cortex. Small numbers of necrotic cells were scattered through the adrenal cortex.

ACI and Maxx rats, which died later than Brown Norway or Wistar-Furth rats with symptoms suggesting central nervous system involvement, were affected by mild to severe necrotizing encephalitis and encephalomyelitis. There was no predilection for

TABLE II. Histopathologic and Virologic Findings in Moribund Rats

			Histopathology[b]						
			Liver	Brain					
Rat strain	Virus dose[a]	Day of death	Necrosis	Necrosis	Mononuclear infiltrates	Log_{10} pfu/gm or ml Brain	Liver	Blood	PRN_{80} titer
Wistar-Furth	3.7	2	3	0	0	6.9	8.5	10.1	–
	3.7	3	2	0	0	3.5	7.3	8.7	–
	3.7	3	3	0	0	3.9	6.2	6.9	–
	3.7	3	3	0	0	–[c]	–	–	–
Brown Norway	5.7	3	3	0	0	–	–	–	–
	3.7	2	3	0	0	3.5	3.9	6.4	–
	3.7	2	3	0	0	2.7	5.8	5.6	–
	3.7	2	3	0	0	–	–	–	–
ACI	5.7	14	0	3	3	6.3	< 1.7	< 1.7	≥ 160
	5.7	15	0	3	1	5.5	< 1.7	< 1.7	≥ 160
	5.7	18	1	3	2	3.5	< 1.7	< 1.7	≥ 160
	3.7	14	0	2	1	5.5	< 1.7	< 1.7	≥ 160
Maxx	5.7	10	0	3	0	5.4	< 1.7	< 1.7	≥ 160
	5.7	15	0	3	2	1.7	< 1.7	< 1.7	≥ 160
	3.7	10	0	3	0	5.6	< 1.7	< 1.7	≥ 160

[a] Log_{10} pfu injected subcutaneously on day 0.
[b] 0, None or minimal; 1, mild; 2, moderate; and 3, severe lesions.
[c] Not measured.

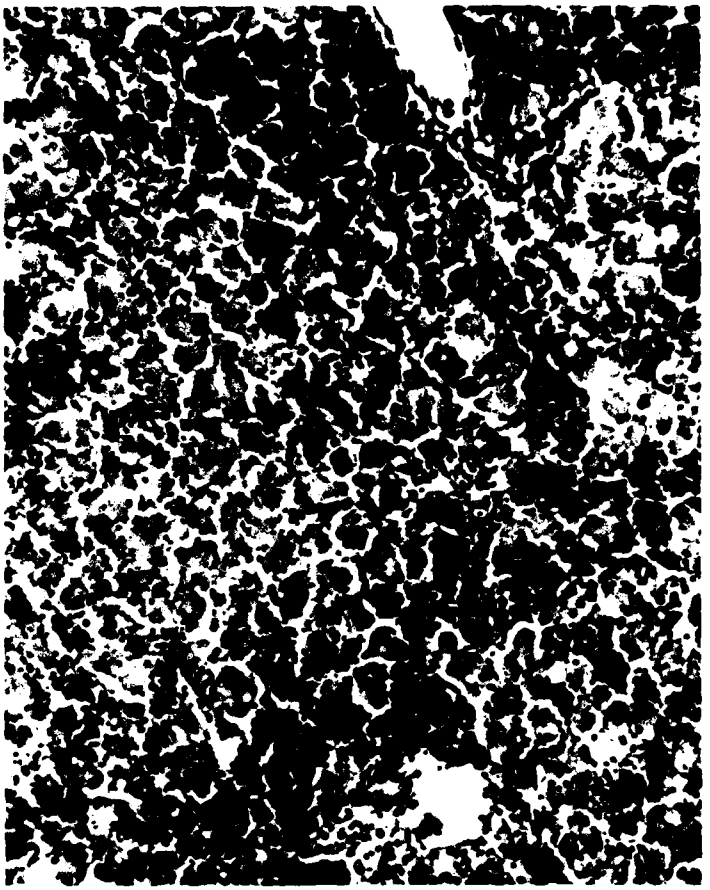

Fig. 1. Brown Norway rat day 2. Severe hepatocellular necrosis with marked congestion or pooling of blood. 200 ×.

any portion of the central nervous system; however, the cerebellum was consistently least affected. Lesions were characterized by focal areas of neuronal necrosis of variable size with marked neutrophilic infiltrate (Fig. 2). Additionally, mild to moderate perivascular cellular infiltrates, comprised primarily of lymphocytes, were scattered throughout the brain and spinal cord. Lesions were not seen in peripheral nerves. The only additional lesions seen in these animals were lymphoid depletion and necrosis of the thymic cortex.

Virological studies were performed in many of the animals necropsied (Table II). Rats dying of hepatic necrosis uniformly had large quantities of virus in the liver and blood. Their brain virus titers may well reflect contamination with blood. Encephalitic rats, however, did not have detectable quantities of virus in blood or liver. In spite of the presence of serum neutralizing antibody, it was usually possible to measure 5 to 6 log pfu/gm of brain tissue.

Initial studies indicated at least a 100-fold difference between the lethality of RVF virus for rats susceptible to hepatic necrosis and more resistant strains. Ten-fold increments of virus were titrated using groups of five susceptible Wistar-Furth rats. The LD_{50} was 3 pfu and the pattern of death was very similar to that seen with higher doses;

Fig. 2. Maxx rat day 15. Cerebrum. Large area of necrosis with marked neutrophilic infiltrate. Both neurons and neutrophils are necrotic. 200 ×.

survival was not prolonged past 3 to 4 days even at limiting dilutions. Resistant Lewis rats were also inoculated with 6.7 log pfu; two of five succumbed on days 8 and 15 with the clinical picture of encephalitis, while none of five receiving 7.7 log pfu died.

When ACI or Maxx rats were inoculated sc with 3.7 log pfu mortalities of 10 to 50% were obtained, but increasing the virus dose 100-fold failed to kill all the animals (Table I). We therefore attempted to manipulate the infection to obtain a more uniform outcome by injecting a larger dose of challenge virus (Table IIIa), using virus passed in ACI brain or Wistar Furth serum (Table IIIb,c), or injecting ip or iv (Table IIId,e). There was no increase in the clinical response or mortality.

Direct intracranial injection of $10^{6.4}$ pfu resulted in death of all three rats, but survival was only 4 to 6 days and the histological picture was one of focal cerebral necrosis with a scanty local polymorphonuclear infiltrate. We also injected five Lewis rats (resistant to sc inoculation) intracranially with 50 pfu and all succumbed to encephalitis between days 4 and 7.

TABLE III. Effects of Virus Dose, Passage History and Route of Inoculation on Lethality of the ZH-501 Strain of RVFV for ACI Rats

Passage of inoculum	Log dose (pfu)	Route	Survivors/inoculated
a) $(FRL)_2$[a]	7.7	sc	7/7
b) $(FRL)_2$ (ACI brain)[b]	4.7	sc	4/4
c) $(FRL)_2$ (Wistar-Furth serum)[b]	5.7	sc	3/5
d) $(FRL)_2$	5.7	ip	6/8
e) $(FRL)_2$	5.7	iv	1/4

[a]Second fetal rhesus lung passage.
[b]Additional passage in rat brain or serum.

DISCUSSION

RVF has been recognized as a veterinary and medical problem in Africa for half a century but has received relatively little attention in the biomedical literature. This is owing in part to the success with which inexpensive live-attenuated vaccines have limited the economic inroads of epizootics. Nevertheless, events of the last few years have made it clear that a) RVF is widely distributed throughout sub-Saharan Africa and is not confined to the great Rift Valley [Peters and Meegan, 1981]. b) The virus can be introduced into previously uninvolved areas, exemplified by Egypt, and cause devastating human and animal disease [Laughlin et al, 1979; Meegan et al, 1979; World Health Organization, 1979]. Our ability to control such an extension is limited [Peters and Meegan, 1981]. c) Human infection is not always manifest as a self-limited febrile illness with the occasional complication of retinal lesions [Schrire, 1951; Cohen and Luntz, 1976; Mahdy et al, 1979; Siam et al, 1979; Deutman and Klomp, 1981]. It may be associated with severe and fatal hemorrhagic fever or encephalitis [Van Velden et al, 1977; Laughlin et al, 1979; Maar et al, 1979; Sanepoel et al, 1979; World Health Organization, 1979]. These changing perceptions of the potential of RVF led us to examine the pathogenicity of the Egyptian Zagazig Hospital 501 strain of RVF virus for laboratory animals and resulted in the recognition of the widely differing responses of inbred rat strains to infection.

Several inbred rat strains were largely resistant to clinical disease after RVFV inoculaion (Fischer 344, Buffalo, Lewis, DA). The most striking contrast was seen after infection of Wistar-Furth and Brown Norway rats; they died within 4 days after inoculation with virtually complete hepatic necrosis. In quantitative comparisons Lewis rats were a million-fold more resistant than Wistar-Furth rats. Viremia titers and histologic lesions of Wistar-Furth and Brown Norway rats resembled those described in hamsters, mice, and sheep dying with RVF [Daubney et al, 1931; Findlay, 1932; Easterday, 1965]. Humans dying with hemorrhagic fever are also viremic and have extensive liver damage [Van Velden et al, 1977; Abdel-Wahab et al, 1978; Imam et al, 1979; Laughlin et al, 1979; Swanepoel et al, 1979; Meegan and Shope, 1981]. Relatively little is understood about the degree of peripheral vascular damage in humans, but the extensive occurrence of petechiae and mucous membrane bleeding suggests that it may be more prominent than in the rat and autopsies suggest that liver necrosis may be less extensive than in the laboratory rat infection.

Other inbred rats (ACI, MAXX) survived the first week of infection but then developed clinical and histological evidence of encephalitis. The animals were no longer

viremic at that time but had circulating neutralizing antibody. The brain, however, contained high titers of virus. Since the encephalitis occurred late after infection (mean time to death, 11 to 16 days for different experimental groups), one might speculate that the antiviral immune response or an induced autoimmune phenomenon was responsible. However, the necrotizing histological lesion suggests a direct viral cytopathic effect. Introduction of virus into the brain results in death within only 4 to 7 days. Perhaps after sc inoculation entry of virus into the brain was delayed or the course of illness modulated by the immune response to RVFV. This type of lesion has been reported in the occasional RVF-infected mouse that survives acute hepatic necrosis [Findlay and MacKenzie, 1936; Peters and Anderson, 1981], in kittens or puppies [Mitten et al, 1970], or in certain rodent species, such as Sigmodon hispidus, Calomys callosus, and Meriones unguiculatus [Peters and Anderson, 1981; Slone, T. W., A. De Paoli, and C. J. Peters, Pathology and Pathogenesis of Rift Valley fever infection of laboratory rodents, in preparation, 1982]. The single published description of a human brain with RVF encephalitis [Van Velden et al, 1977] is rather brief but appears to be in accord with the experimental findings. It is noteworthy, however, that human encephalitis (as well as retinitis) occurs after the acute illness; patients present to hospital with high-titered serum antibody [Schrire, 1951; Maar et al, 1979; Siam et al, 1979; Meegan and Shope, 1981].

The three disparate responses observed in these inbred rat strains almost certainly resulted from genetic differences among the hosts. All three clinical syndromes were seen in inbred rats from a single commercial source; and in the two cases tested, resistant or RVF-encephalitis prone rat strains obtained from another colony responded in a similar fashion. Preliminary breeding studies with Lewis and Wistar-Furth rats suggested that inheritance of resistance to fulminant infection can be examined by classical techniques and may be a Mendelian dominant trait [Peters and Anderson, 1981].

Although many aspects of the rat immune response are under genetic control [Gasser, 1977], it is unlikely that classical T or B cell elements play the major role in determining survival, since fulminant hepatic infection led to death after only 3 to 4 days. Additional evidence against the humoral antibody response as the major determinant of hepatic necrosis comes from the observation that resistant (Lewis) or susceptible (Brown Norway) rats developed similar PRN titers after inoculation of formalin-inactivated RVF vaccine (C. J. Peters and A. O. Anderson, unpublished data). The gene or genes that determine resistance do not act by preventing viral replication at the cellular level; fibroblast cultures fom both Lewis and Wistar-Furth rats supported virus growth to high concentrations although detailed quantitative studies are still in progress (J. Rosebrock and C. J. Peters, unpublished observations). Nor is there a general susceptibility of certain rat stains to encephalitis, since inoculation of inbred rat strains with Venezuelan encephalitis virus resulted in a completely different susceptibility profile (P. B. Jahrling and C. J. Peters, unpublished data).

Neither the genetic determinants nor the pathogenesis of the encephalitis is entirely clear. Resistant Lewis rats inoculated intracerebrally with only 50 pfu all developed encephalitis, so the critical element presumably lies in entrance of the virus to the nervous system. It proved to be difficult to develop a uniformly lethal encephalitis model by changing rat strains, increasing virus dose, manipulating route of inoculation, or using rat-brain passaged virus. The reasons for this were not established.

Several experimental models are known in which a particular host's genetic constitution results in a lethal outcome from acute viral infection [Bang, 1978]. The

RVFV-infected rat is unusual in that, in addition to resistant strains, there are susceptible genotypes that result in two different outcomes: fulminant infection and encephalitis. Further exploration of the rat model seems desirable, since the widely divergent outcomes suggest that very different pathogenetic mechanisms may be operative. These mechanisms may be relevant to understanding the genesis of the human clinical syndromes of benign infection, hemorrhagic fever, and encephalitis, which to some extent resemble the different patterns observed in RVFV infection of genetically distinct inbred rat strains. Whether or not the same critical differences leading to hemorrhagic fever or encephalitis exist in rat and man and whether or not they are also genetically determined in man, this model illustrates the potential importance of host genes in explaining distinct responses to infection with a single agent.

REFERENCES

Abdel-Wahab KSE, El Baz LM, El Tayeb EM, Omar H, Ossman MAM, Tasin W (1978): Rift Valley fever virus infections in Egypt: Pathological and virological findings in man. Transactions of the Royal Society of Tropical Medicine and Hygiene 72:392–396.

Bang FB (1978): Genetics of resistance of animals to viruses: I. Introduction and studies in mice. Advances in Virus Research 23:270–348.

Bishop DHL, Calisher CH, Casals J, Chumakov MP, Gaidamovich SYa, Hannoun C, Lvov DK, Marshall ID, Oker-Blom N, Pettersson RF, Porterfield JS, Russell PK, Shope RE, Westway EG (1980): Bunyaviridae. Intervirology 14:125–143.

Cohen C, Luntz MH (1976): Rift Valley fever and rickettsial retinitis including fluorescein angiography. Klinische Monatsblaetter fur Augenheilkunde 169:685–699.

Daubney R, Hudson JR, Garnham PC (1931): Enzootic hepatitis or Rift Valley fever: An undescribed virus disease of sheep, cattle and man from East Africa. Journal of Pathology and Bacteriology 34:545–579.

Deutman AF, Klomp HJ (1981): Rift Valley fever retinitis. American Journal of Ophthalmology 92:38–42.

Easterday BC (1965): Rift Valley fever. Advances in Veterinary Science 10:65–127.

Findlay GM (1932): Rift Valley fever or enzootic hepatitis. Transactions of the Royal Society of Tropical Medicine and Hygiene 25:229–265.

Findlay GM, MacKenzie RD (1936): Studies on a neurotropic Rift Valley fever virus: "Spontaneous" encephalomyelitis in mice. British Journal of Experimental Pathology 17:441–447.

Gasser DL (1977): Current status of rat immunogenetics. Advances in Immunology 25:93–139.

Imam IZE, Darwish MA, El-Karamany R (1979): An epidemic of Rift Valley fever in Egypt. I. Diagnosis of Rift Valley fever in man. Bulletin of the World Health Organization 57:437–439.

Laughlin LW, Meegan JM, Strausbaugh LJ, Morens DM, Watten RH (1979): Epidemic Rift Valley fever in Egypt: Observations of the spectrum of human illness. Transactions of the Royal Society of Tropical Medicine and Hygiene 73:630–633.

Maar SA, Swanepoel R, Gelfand M (1979): Rift Valley fever encephalitis: A description of a case. Central African Journal of Medicine 5:8–11.

Mahdy MS, Bansen E, Joshua JM, Parker JA, Stuart PF (1979): Potential importation of dangerous exotic arbovirus diseases. A case report of Rift Valley fever with retinopathy. Canadian Disease Weekly Report 5:189–191.

Meegan JM (1979): The Rift Valley fever epizootic in Egypt 1977–1978. I. Description of the epizootic and virological studies. Transactions of the Royal Society of Tropical Medicine and Hygiene 73:618–623.

Meegan JM, Shope RE (1981): Emerging concepts on Rift Valley fever. Perspectives in Virology 11:267–287.

Mitten JQ, Remmele NS, Walker JS, Carter RC (1970): The clinical aspects of Rift Valley fever virus in household pets. III. Pathologic changes in the dog and cat. Journal of Infectious Diseases 121:25–31.

Murphy FA, Harrison AK, Whitfield SG (1973): Bunyaviridae: Morphologic and morphogenetic similarities of Bunyamwera serologic supergroup viruses and several other arthropod-borne viruses. Intervirology 1:297–316.

Peters CJ, Anderson GW Jr (1981): Pathogenesis of Rift Valley fever. Contributions to Epidemiology and Biostatistics 3:21–41.

Peters CJ, Meegan J (1981): Rift Valley Fever. In: Beran GW (ed): "CRC Handbook Series in Zoonoses, Section B: Viral Zoonoses." Boca Raton, Florida: CTC Press, vol 1, pp 403–420.

Rice RM, Erlick BJ, Rosato RR, Eddy GA, Mohanty SB (1980): Biochemical characterization of Rift Valley fever virus. Virology 105:256–260.

Schrire L (1951): Macular changes in Rift Valley fever. South African Medical Journal 25:926–930.

Shope RE, Peters CJ, Walker JS (1980): Serological relation between Rift Valley fever virus and viruses of phlebotomus fever serogroup. Lancet 1:886–887.

Siam AL, Meegan JM, Gharbawi KF (1979): Rift Valley fever ocular manifestation: Observations during the 1977 epidemic in the Arab Republic of Egypt. British Journal of Ophthalmology 64:366–374.

Swanepoel R, Manning B, Watt JA (1979): Fatal Rift Valley fever of man in Rhodesia. Central African Journal of Medicine 25:1–8.

Van Velden DJJ, Meyer JD, Olivier J, Gear JHS, McIntosh B (1977): Rift Valley fever affecting humans in South Africa: A clinicopathological study. South African Medical Journal 51:867–871.

World Health Organization (1979): Rift Valley fever surveillance. Weekly Epidemiological Record 54:293–294.

Accession For
NTIS GRA&I ☑
DTIC TAB ☐
Unannounced ☐
Justification
By
Distribution/
Availability Codes
Dist | Avail and/or Special
A | 21

DTIC COPY INSPECTED