Problems of the arthropod-borne viruses in Africa

BY

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The great majority of viruses which produce encephalitis in man and domestic animals are arthropod-borne and the present discussion will be limited to those which fall into this group. In addition to being arthropod-borne and encephalitogenic, these agents have other characteristics in common, one of which is that only a small percentage of the individuals whom they attack suffer encephalitis as a result; instead, most of the victims suffer an acute but self-limited illness not characterized by neurological symptoms. In some instances the effects in man are completely sub-clinical. The encephalitogenic viruses are closely related to others which, though neurotropic in experimental animals, are viscerotropic in human beings, yellow fever and Rift Valley fever viruses being examples. Thus all, or nearly all, the arthropod-transmitted viruses have neurotropic properties, but man is resistant to the neurotropic action of many of the agents. From the point of view of the virologist and the epidemiologist, the problems which these agents present are similar, whether or not the attack of the agent in man is centered upon the nervous system.

The complexity of the problem of the arthropod-borne viruses in Africa immediately becomes apparent when one attempts to make a list of the agents which are active in this continent. In West Africa, where the first experimental work in this field was done, the actual virus isolations have included yellow fever, Zika and Semliki Forest viruses. In East Africa all three of these agents are likewise present, but in addition the following viruses have been isolated : Chikungunya, West Nile, Ntaya, Uganda S, Rift Valley fever, Bwamba fever and Bunyamwera. Each of these is known or believed to be a human pathogen. In Egypt, 3 different arthropod-borne agents have been isolated including West Nile,

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Sindbis and Sandfly fever viruses. In South Africa the list is even greater, the following having been isolated from man, from arthropod hosts, from animals or from various of these sources: Sindbis, Chikungunya, Middelburg, a virus yet unnamed which we call AR 136, another of human origin which we call H 336, Spondweni, Wesselsbron, Rift Valley fever, Pongola, Bunyamwera and Simbu. These viruses isolated in various parts of Africa are set forth in Table I and are divided into the serological groups into which they fall. As may be seen, 5 of them apparently belong to Casals' group A, 8 belong in Casals' group B and 6 have not been classified by hemagglutination either because the antigen which is produced does not induce hemagglutination, or the hemagglutinogen produced has not been shown to have any relation te antigen produced by other viruses. It is obvious, therefore, that the list of arthropod-borne viruses which attack man in Africa, not only is large, but the agents which are included in it are extremely varied and the problems in consequence complex.

TABLE I.

Viruses in Africa known or believed to be arthropod-borne and pathogenic for man.

Serologic group (*)	Virus	Isolations			
		E. Africa	W. Africa	Egypt	S. Africa
A	Semliki Forest	×	×	—	—
	Sindbis	—	—	×	×
	Chikungunya	×	—	—	×
	Middelburg	—	—	—	×
	AR 136 (**)	—	—	—	×
B	Yellow fever	×	×	—	—
	West Nile	×	—	×	—
	Ntaya	×	—	—	—
	Zika	×	×	—	—
	Uganda S	×	—	—	—
	H 336	—	—	—	×
	Spondweni	—	—	—	×
	Wesselsbron	—	—	—	×
Unclassified	Rift Valley fever	×	—	—	×
	Bwamba fever	×	—	—	—
	Pongola	—	—	—	×
	Bunyamwera	×	—	—	×
	Simbu	—	—	—	×
	Sandfly fever	—	—	×	—

(*) Casals' classification by hemagglutination-inhibition.
(**) Not proved to be in group A but behaves like others in this group.

The evidence of virus activity which we have just considered is based on isolations of the agents from human, animal or arthropod sources. In addition to this there is a great deal of information concerning the distribution of virus diseases in Africa in the results of serological tests on sera from human beings, domestic animals, wild animals and birds. As example of how slowly our knowledge of these agents develops let us consider Bunyamwera virus for a moment. This virus was first isolated nearly 15 years ago from *Aedes* mosquitoes caught by Haddow in an uninhabited area of the Semliki Forest. Protection tests on human sera indicated that the agent attacks man in East Africa, but our only knowledge of its actual effects in man were based on experimental studies of its oncotropic effects. It was found that the virus can cause severe encephalitis in man. Later, antibodies for this virus were found in human sera in South Africa, and in 1955 the virus was isolated from mosquitoes caught in the lowlands on the east coast of the Union. Since then we have made further isolations of the agent from mosquitoes, but it was not until May 1957 that the agent was isolated from a naturally infected human being. There can no longer be doubt of its pathogenicity for man, and our surveys indicate that it is very prevalent in certain areas.

When one considers the vectors which are responsible for the transmission of these 19 or so different agents on the African continent, the problem is seen to be further complicated. Table II is a list of the mosquitoes which are known to be responsible for the transmission of the above mentioned viruses, or from which these agents have been isolated in one or more parts of Africa. If each of these may be regarded as a vector in the true sense, and many of them have been proved to be, the list of mosquitoes which are responsible for the transmission of these agents includes at least 10 species of the genus *Aedes*, 1 of *Eretmapodites*, 1 of *Taeniorhynchus* and at least 4 of the genus *Culex*. Some of the species listed have been associated with only 1 virus. Others, such as *Aedes aegypti*, have been definitely associated with 2 or 3 different viruses and *Aedes circumluteolus* has been associated with no less than 7 different viral species. It is, furthermore, well known that some viruses, yellow fever for example, may be transmitted under one circumstance by one mosquito, and in another by a completely different species. Wesselsbron virus, discovered in South Africa only two years ago, has already been definitely associated with at least 3 different mosquito species, and the actual vector relationship of 2 of these is proved beyond question.

TABLE II.

Mosquitoes implicated as vectors by transmission experiments, or as hosts by isolation of virus from them.

Species	Implicated by		Number of viruses
	Transmission	Isolation	
Aedes (*Stegomyia*) *aegypti*	×	×	3
Aedes (*Stegomyia*) *simpsoni*	×	×	1
Aedes (*Stegomyia*) *africanus*	×	×	4
Aedes (*Stegomyia*) *de-boeri*	—	×	1
Aedes (*Aedimorphus*) *abnormalis* ...	—	×	1
Aedes (*Aedimorphus*) *albocephalus*...	—	×	1
Aedes (*Aedimorphus*) *tarsalis* group .	—	×	1
Aedes (*Banksinella*) *circumluteolus* ...	×	×	7
Aedes (*Banksinella*) species	—	×	2
Aedes (*Ochlerotatus*) *caballus*	×	×	3
Aedes species	—	×	1
Eretmapodites species	×	×	2
Taeniorhynchus (*Mansonioides*) *uniformis*	—	×	2
Culex (*Culex*) *univittatus*	×	×	3
Culex (*Culex*) *antennatus*	—	×	1
Culex (*Culex*) *theileri*	—	×	1
Culex tigripes or *annulioris*	—	×	1

Many of the arthropod-borne viruses which attack human beings have important other hosts than man. In some instances, the non-human host is, without question, the natural vertebrate host of the agent. In yellow fever, for example, it is well-known that infection in man is much less common than infection in the natural wild hosts, monkeys. The disease in monkeys is extremely prevalent, and ever-present in many forested localities, yet the virus gains access to the human host only when a whole series of circumstances are more or less accidentally right at the same time. Mammals or birds which are susceptible to the arthropod-borne viruses that attack man, may be important to man in any one of several different ways. For instance, if the extra-human host is a domestic animal, say sheep, the susceptibility of the species may be of great importance to man in having an important bearing on his livelihood or upon his source of food. If the extra-human host of a virus is a non-migratory bird then this may be important to man in that the infection cycle will be initiated in man only when there is concomitant or preceding infection in a new generation of nestling birds and simultaneously present a species of vector insect which feeds on both birds and human beings. Birds may be of great importance otherwise in transporting virus infections from one region to another.

When one considers the infection rate in man or in domestic animals or wild hosts, one usually thinks of the infective agents as being more or less ever-present in a given region and productive of endemic or enzootic outbreaks, or else one regards these agents as being only occasionally active, then in epidemic or epizootic form. It is not common to consider that a number of different infective agents of similar nature may be active in the same region at the same time, and possibly transmitted by the same vectors. This, however, can take place as was found in the coastal lowlands of northern Natal in 1955. There in a single month, six different viruses were isolated from mosquitoes and 5 of these came from the same species of mosquitoes (Table III). More recently still, we have found 2 different agents present in another locality at the same time, and have conclusively demonstrated the presence of both agents in pools containing no more than 50 mosquitoes. This, of course, does not prove that a single mosquito can simultaneously harbour more than one virus, but this possibility does exist.

Climatic factors are of great importance in infection cycles with these agents. Arthropod-borne viruses can and do occur in regions where the temperature at times falls to below freezing and mosquito activity is reduced to a negligible level. Frost *per se* does not eliminate either the virus or the vector in the absolute sense. Transmission cycles during severe winter weather may entirely cease, but if infected vectors survive, transmission may be resumed when the weather conditions again become suitable for their activity. This is precisely the situation which takes place in the western United States each year with reference to infection with western equine encephalomyelitis and St. Louis encephalitis viruses.

TABLE III.

Viruses isolated in Tongaland, 1955.

Strain	Source	Identity
AR 1	*Aedes (Banksinella) circumluteolus*	New, but related to Bwamba fever virus
AR 31	*Aedes (Banksinella) circumluteolus*	
AR 37	*Aedes (Banksinella) circumluteolus*	
AR 64	*Aedes (Banksinella) circumluteolus*	
AR 96	*Aedes (Banksinella) circumluteolus*	
AR 107	*Aedes (Banksinella) circumluteolus*	
AR 108	*Aedes (Banksinella) circumluteolus*	
AR 110	*Aedes (Banksinella) circumluteolus*	
AR 115	*Aedes (Banksinella) circumluteolus*	
AR 117	*Aedes (Banksinella) circumluteolus*	
AR 11	*Aedes (Banksinella) circumluteolus*	Bunyamwera virus
AR 53	*Aedes (Banksinella) circumluteolus*	New virus
AR 74	*Aedes (Banksinella) circumluteolus*	Mixture, Bunyamwera and RVF
AR 94	*Taeniorhynchus (Mansonioides) uniformis*	New virus
AR 100	*Aedes (Banksinella) circumluteolus*	Probably identical with Wesselsbron virus.
H 177	Blood of febrile patient	
AR 118	*Aedes (Banksinella) circumluteolus*	Rift Valley fever virus

The method by which overwintering of virus takes place under these circumstances is not entirely clear. The only positive information which exists indicates that the virus survives through the winter in the adult vector. The latter may be unable to propagate during the winter months and its vitality may be so reduced that it is incapable of transmitting the infection at this time, but it may serve as a reservoir in which the virus remains alive from one season to the next. In the Orange Free State in 1956, for example, a certain *Culex* species which was the only mosquito present during a very big epizootic of Rift Valley fever, and from which the virus of that disease was twice isolated, was later found to be present in dead winter after many weeks of freezing weather, but only, of course, in very small numbers.

Temperature may be of importance in another respect. The intrinsic period of incubation in the mosquito varies with the temperature and in the event a mosquito became infected and the temperature was thereafter for some days quite low, it is possible that the intrinsic incubation period could be so prolonged that the mosquito would never become capable of transmitting the virus, although the reverse would be true were the weather warmer. Excessive heat may also be unfavorable to the vector as there is evidence that mosquitoes are less long-lived when the temperature is excessively hot than when it is more moderate. Likewise, rainfall can be favorable or unfavorable to the vector. In the event there is too little precipitation, breeding foci for the arthropods may dry up, but if there is too much rainfall certain of the breeding foci, tree-holes for example, may be less effective than otherwise because of the fact that the immature stages of the mosquitoes are washed away before they have opportunity to mature.

Altitude may be of importance to infection cycles with certain arthropod-borne viruses. In western Uganda, for instance, Haddow and his associates found that infection with yellow fever virus did not apparently occur in human beings above 5,000 ft. In that particular instance, there was apparently an easy explanation for this fact in that the principal vector did not occur above that altitude. In other regions there may be great differences in the incidence of virus disease at different altitudes without the explanation of this fact being so easily obtainable. In northern Natal, for instance, we have studied the incidence of infection with a number of different viruses in the coastal lowlands from sea level to about 500 ft., as compared with the nearby highlands at approximately 2,000 ft. The immunity rate to various viruses was higher in the lowland than in the highland localities (Table IV).

However, the vectors which are known or believed to be responsible for transmission are present in both these zones. It is, of course, possible that the number of vector insects present is the important factor and it is certainly true that the prevalence of vectors in the lowlands is much greater than in the highlands.

TABLE IV.

Immunity to two viruses among children and adults of lowland and highland areas.

Area of residence	Age of donors, years	Immune to AR 1		Immune to H 177	
		Ratio	Per cent	Ratio	Per cent
Lowlands	0 - 14	37/110	33.6	17/110	15.5
	15 +	51/131	38.9	61/131	46.6
Highlands	0 - 14	1/44	2.3	1/44	2.3
	15 +	2/52	3.8	2/52	3.8

Climatic factors and/or vegetation may be important in a different sense than those yet considered. Information bearing on such facts has been obtained at our field station in northern Natal. The whole study area of this field station is at approximately the same altitude and in it the rainfall is more or less uniform. However, we have found that in the immediate vicinity of our camp the infection rate with several different viruses, although high, is nevertheless significantly lower than it is in another area no more than 5 miles away. In the camp area the infection rate with 2 group B viruses in children was 4.4 per cent, in adults 26.5 per cent. In the other area only 5 miles away the immunity rate in children was 22 per cent and in adults 54 per cent (Table V). Although these two regions are similar in rainfall, altitude and so forth, they do have features which are different. In the camp area the vegetation is low scrub and thornbush. In the Gumede's Kraal area, where the infection rate is much higher, the vegetation is tall grass, savannah type, and the explanation for the higher incidence of infection in the one zone than in the other has apparently been obtained. In the winter months of 1956 *Aedes* *circumluteolus,* the mosquito which is responsible for the transmission of several viruses in this area, fell to a very low level in the immediate environs of the camp and very few of them could be taken in intensive catches. During this same period a 2-hour catch at Gumede's Kraal in the afternoon yielded 45 of these mosquitoes. Included in this number were several which were obviously recently emerged and some which had recently fed. From this it was evident that winter propagation of the vector was taking place in this small localized area. Thus it appears that in this generally favorable broad area of the coastal lowlands, there may be small zones especially suited to winter propagation of arthropods which then serve as seed beds for supplying vectors and virus to neighboring zones when climatic conditions again become favorable for arthropod propagation.

TABLE V.

Incidence of neutralizing antibodies (*) in man and of the vector *Aedes circumluteolus* in 2 nearby areas.

	Ndumu Camp area	Gumede's Kraal area
Antibodies in children (**)	4.4 %	22.2 %
Antibodies in adults (**)	26.5 %	54.5 %
A. circumluteolus, Winter '56.	Very scarce	Plentiful

(*) For 2 group B viruses isolated in this region.
(**) Groups for the two localities standardized as to age.

Clinical problems associated with the arthropod-borne viruses.

Some of the agents with which we are concerned are real killers and we have to take measures against them in order to avoid their lethal effects. The majority, however, do not cause high mortality and, so far as man is concerned, the problem is to avoid the ill effects which some of these agents leave in the recovered human hosts, and to lessen the number of acute diseases to which man is subject. Rift Valley fever in man, for instance, often produces serious eye complications, including blindness. Certain of the arthropod-borne encephalitides, western equine, for example, also leave the recovered human host with residual neurological effects from which he does not recover, especially if he is a child. Notable among these is the convulsive state. It has recently been found that children who suffer from convulsions during the acute illness are subject throughout their after-lives to convulsions even though they may have completely recovered in other respects. This particular disease is notorious also for causing serious mental retardation in children who have been infected by it.

Fortunately for man the great majority of infections with the arthropod-borne viruses do not have these untoward after effects. The common circumstance is for man to have an acute illness with sudden onset, and more or less severe clinical course of 3 to 7 or 8 days duration, followed usually by prompt convalescence without any noteworthy after effects. The net effect, therefore, is to incapacitate the individual for no more than a week or two and to leave him as well as he was before he became ill. But this suffering and loss of time is important, especially since large numbers of individuals may become simultaneously infected.

Many of the viruses which attack man also attack domestic animals. Table VI shows evidence obtained in immunity surveys of the frequency with which 2 viruses attack both man and domestic animals in the lowland areas of northern Natal. The importance of these agents to man lies in the fact that the domestic animal may by affected in any one of several different ways :

1. It may die;
2. If it is a pregnant female it may abort and the offspring be lost;
3. If the animal host is a bovine, lactation may be terminated with resultant serious economic effects;
4. Whatever species of animal is involved, its weight gain is likely to be arrested and if it is a wool-bearing animal the fleece may be affected.

Farmers who have faced these problems have been among our most enthusiastic collaborators.

Control of the diseases.

Vaccination. — Several of the arthropod-borne viruses have already been modified in such fashion that a living attenuated form of the agent may be successfully used as a vaccine. Yellow fever is an example of this, and in South Africa the attenuated neurotropic form of Rift Valley fever virus has also gained widespread use in veterinary circles. Attempts have also been made to produce effective killed vaccines with some of these neurotropic viruses but the results have not been conspicuously successful. Some of these agents can be modified, either by animal passage, or by chick embryo cultivation, or by growing them in tissue culture, and it

TABLE VI.

Immunity to two recently isolated viruses in Tongaland.

Area of Residence	Results	Human beings		Cattle		Sheep		Goats	
		AR 1	H 177	AR 1	H 177	AR 1	H 177	AR 1	H 177
Tongaland, Lowlands	Protective, ratio	88/241	78/241	24/135	66/134	12/63	17/63	25/80	44/80
	Protective, %	36.5	32.4	17.8	49.3	19.0	27.0	31.2	55.0
Tongaland, Highlands	Protective, ratio	3/96	3/96	0/39	7/28	0/50	3/46	0/30	4/20
	Protective, %	3.1	3.1	0	25.0	0	6.5	0	20.0

would seem that as far as vaccines are concerned, the greatest hope lies in producing attenuated virus for immunization.

Vector control. — The problem of vector control, if it can be conquered, has certain distinct advantages over vaccination. Notable among these is that in regions where a number of arthropod-borne viruses are prevalent, control by vaccination requires the use of several different vaccines, whereas effective control of vectors might eliminate the necessity for any vaccine. However, among the vectors of the viruses with which we are concerned there are mosquitoes which breed in all sorts of places, some of them in ground pools, some in tree holes, etc., and control is by no means a simple problem. There is the further complication that many insects, as we now know, acquire resistance to certain of the newer insecticides. Where ground pool breeders are the principal vectors it is possible that dredging and grading might also have value in control of vectors. However, it suffices to say that neither in vector control, nor in vaccination, nor in the care of the patient do we yet have any panacea which will enable us to bring this group of diseases under control; nor does it seem likely that those of us who are engaged in research on these problems are likely to find all the answers in the near future.