LYMPHOCYTIC CHORIOMENINGITIS IN THE SYRIAN HAMSTER

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The Syrian hamster (*Cricetus auratus*) has been shown to be highly susceptible to St. Louis (1, 2) and to Japanese (2) encephalitis. Since this animal is now readily available in the United States for laboratory work, it seemed desirable to test its response to other infectious agents. Our own preliminary observations, like those of Kreis (3), indicated that the virus of lymphocytic choriomeningitis could be recovered from inoculated Syrian hamsters although it caused no apparent clinical disease in them. The intense but silent infection which was subsequently found to occur under these conditions provided an opportunity to study the immunological and pathological response of an apparently healthy host that carried large amounts of virus. The importance of this type of silent infection as a reservoir for the spread of diseases as diverse as lymphocytic choriomeningitis (4, 5), yellow fever (6), psittacosis (7), rabies (8), pseudorabies (9), Russian encephalitis (10), Q fever (11, 12), and sylvatic plague (13) has been pointed out by workers in these fields and discussed by Andrewes (14) and by Meyer (15). The inapparent infection of hamsters with the virus of choriomeningitis should be of interest to laboratory workers because of the possibility that this agent might be carried as a contaminant during the passage of other neurotropic viruses. The present communication reports the results of work dealing with the distribution and persistence of virus in hamsters, and with the serological response of this host to infection. In addition, observations are presented concerning the simultaneous infection of the hamster with a mixture of the viruses of lymphocytic choriomeningitis and St. Louis encephalitis.

Materials and Methods

Hamsters.—Young adult Syrian or golden hamsters (*Cricetus auratus*) were employed. The animals bred at The Rockefeller Institute were kept under strict isolation until they were 4 to 6 months old at which time they weighed 100 to 150 gm. each.

Virus.—Brain tissue of a guinea pig infected with the 92nd guinea pig passage of the W.E. (16) strain of choriomeningitis virus was used to initiate infection in hamsters. The Hubbard strain of St. Louis encephalitis virus, isolated in 1937 (17), was employed; this agent had been through 92 serial passages in mice and then 6 passages in Syrian hamsters when given to us by Dr. E. H. Lennette; virus from the 14th passage in hamsters was used.

Antisera.—3 cc. of blood to be tested were obtained by intracardiac puncture from

hamsters held under ether anesthesia. As a rule, the animals were fed only lettuce for a day or so before bleeding in order to lessen the anticomplementary activity of their serum. Specimens of serum, which were often lipemic, were partially clarified by centrifugation at 12,000 R.P.M. for 20 minutes in the cold.

Serological Tests.—The techniques for the complement-fixation (18, 19) and neutralization (19) tests have already been described in detail. The chief features of the former test were the use of 2 units of complement, 2 units of amboceptor, a 5 per cent suspension of washed sheep erythrocytes, and fixation overnight at 3°C. Standard solutions of soluble antigen prepared from infected guinea pig spleens and hyperimmune guinea pig serum were used in the initial tests with hamster immune serum and with extracts of hamster tissue, respectively. The tests were controlled with serum and tissue extracts from normal hamsters. Subsequently, antigen and antibody obtained from hamsters were standardized and employed for the work with hamster material. The neutralization test was carried out in guinea pigs; 4 animals were inoculated subcutaneously with a mixture of the test serum and a virus suspension diluted so that it contained approximately 1000 M.L.D.

Titration of Virus.—Suspensions of material to be tested for virus activity were inoculated intracerebrally into anesthetized Swiss mice. Serial tenfold dilutions of the material were tested, and 0.03 cc. of each dilution were injected into each of 3 mice. The titration end point was regarded as that dilution which killed at least 2 of the 3 mice in a group within 14 days, when the remaining mice were discarded. 10 per cent suspensions of blood and of organs were made on the basis of volume and weight, respectively. Physiological saline solution, pH 7.2, containing 2 per cent normal inactivated guinea pig serum, was used as diluent throughout the titration.

EXPERIMENTAL

Infection of Hamsters with the Virus of Choriomeningitis

Intracerebral or intraperitoneal inoculation of choriomeningitis virus into hamsters resulted uniformly in the appearance of large amounts of the active agent in their blood and organs as early as the 5th day. Furthermore, the agent was regularly detectable in high concentration throughout the body during the 2nd and 3rd weeks after inoculation, and in a few instances it was demonstrable in the brain as late as the 6th and 8th week. The results of a series of titrations in mice of blood, brain, and spleen taken from hamsters at various intervals after inoculation of virus are summarized in Table I. It is apparent from the data presented that during the first 3 weeks of the disease the titer of the blood ranged between 10^3 and 10^5 lethal doses and that the titers of brain and spleen were as high as 10^6 and 10^8, respectively. Additional observations indicate that the liver and lung contained virus in amounts comparable to that found in the blood. Similarly, intratesticular inoculation resulted in a generalized infection; at the end of the 1st week the titer of the testicle was usually lower than that of the spleen from the same animal; *e.g.*, 10^4 lethal doses in the testicle and 10^6 in the spleen. The virus was passed in hamsters through 5 serial transfers from brain to brain at 5 to 7 day intervals;

since it apparently could be carried indefinitely in this host, further passage was not attempted.

Almost all of the hamsters appeared well following inoculation of virus. Among a total of 54 hamsters infected with choriomeningitis virus during the

TABLE I

Distribution and Persistence of Virus in Hamsters and Their Antibody Response to Infection with Lymphocytic Choriomeningitis

Hamster*	Time after inoculation	Appearance	Titer of virus			Antibody tests	
			Blood	Brain	Spleen	Complement-fixing	Neutralizing
1-1	5 days	Well	10^{-4}	10^{-4}	10^{-6}‡	Not done	Not done
1-6	5 "	"	10^{-5}	10^{-6}	10^{-6}‡	" "	" "
5-10	7 "	"	10^{-3}	10^{-4}	10^{-8}‡	—	" "
5-2, 3	11 "	"	Not done	Not done	Not done	1:32	" "
5-13, 14	14 "	"	10^{-4}	10^{-6}	10^{-5}§	1:16	" "
5-12, 15	21 "	"	10^{-3}	10^{-3}	10^{-3}§	1:32	" "
1-15	22 "	Moribund‖	Not done	10^{-3}	10^{-4}	Not done	" "
5-17	28 "	Well	—	—	—	1:32	—
1-12	28 "	Moribund‖	Not done	10^{-4}	10^{-4}	Not done	Not done
2-2, 3	32 "	Well	" "	Not done	Not done	1:128	—
1-19	35 "	"	10^{-1}	10^{-1}	" "	Not done	—
5-18	35 "	"	—	10^{-2}	—	1:128	Not done
1-20	35 "	"	—	—	—	Not done	—
5-19	42 "	"	—	—	—	1:16	Not done
1-2A	42 "	"	—	10^{-3}	Not done	1:64	+
5-20	49 "	"	—	—	—	1:32	Not done
2-2	53 "	"	Not done	Not done	Not done	1:64	+
1-3	56 "	"	—	10^{-2}	" "	Not done	+
1-17	84 "	"	—	—	—§	1:32	Not done
Pool 2	8 mos.	"	Not done	Not done	Not done	1:32	+

Blood and organs were considered to be non-infectious when mice injected with a 10^{-1} dilution of them remained well; more concentrated suspensions were not tested.

* First number indicates passage; second number indicates animal in passage.

‡ Complement-fixing antigen demonstrable.

§ " " " not demonstrable.

‖ Cross-immunity tests indicated presence of choriomeningitis virus.

course of this work, only 3 became obviously ill; data on 2 of these animals are recorded in Table I. The clinical signs displayed consisted of weakness, conjunctivitis, loss of weight, dehydration, occasionally tremors and, finally, prostration; however, in no instance did the signs develop until 3 to 4 weeks after inoculation. All of the animals in this group of ill hamsters had demonstrable virus in their tissues but only one, 1-15, was free from an obvious bacterial infection; the remaining 2 had an infection caused by an organism

closely related to *Klebsiella capsulata*.[1] While it cannot be said that hamsters never die as a result of infection with the virus of choriomeningitis, it is evident that such an occurrence is rare.

Traub (22) has demonstrated that the urine of mice and of guinea pigs infected with the virus of choriomeningitis is infectious, and Armstrong (23) has stated that the feces of such mice likewise contain the virus. Our preliminary experiments, in which attempts were made to demonstrate the virus of choriomeningitis in urine and feces of infected hamsters, gave irregular results when bacteriologically sterile materials were obtained and tested intracerebrally in mice. The procedures employed to insure bacterial sterility apparently also reduced or destroyed the activity of the virus; consequently, the following experiment was performed.

Urine and feces were collected from 2 hamsters on the 6th day after intracerebral and intraperitoneal inoculations with a suspension of brain from a hamster of the 4th passage. Urine which was obtained by gentle compression of the bladder was collected without fecal contamination. Several pellets of fecal material were removed from the rectum with small forceps; contamination by urine or by capillary hemorrhage was avoided. The fecal material was emulsified in 5 cc. of serum-saline solution and centrifuged 3 times at 2500 R.P.M. for 20 minutes; the opalescent supernatant fluid was transferred to a sterile test tube before the next centrifugation. Urine was centrifuged only once. Cultures of both of the final preparations subsequently revealed the presence of an appreciable number of bacteria. Serial tenfold dilutions of each preparation were made and inoculated subcutaneously into normal guinea pigs; each of 2 animals received 0.5 cc. of each dilution; *i.e.*, 10^{-1} to 10^{-4}. All animals inoculated with the 10^{-1} to the 10^{-3} dilutions of urine and of feces died after exhibiting fever and the usual signs of choriomeningitis; furthermore, one of the animals which received the 10^{-4} dilution of urine succumbed. In order to establish conclusively the etiology of the disease in the guinea pigs, the virus of choriomeningitis was identified in three instances in the following manner.

Blood and splenic tissue from 2 guinea pigs which died after receiving the 10^{-1} and 10^{-2} dilutions, respectively, of urine were bacteriologically sterile. Spleens from both animals were shown to contain the specific soluble antigen of choriomeningitis when tested by complement fixation, and one of the spleens was found to be infectious

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[1] This organism (*Klebsiella capsulata*) apparently causes rather frequent infections in our hamster colony. The most common lesion is a chronic, subcutaneous abscess which often breaks down, forming a draining sinus or a large indolent ulcer. Ultimately death occurs following the development of septicemia, generalized lesions, and cachexia. The most striking of these lesions are areas of acute focal necrosis in the liver which are visible macroscopically and peritonitis and pleurisy with a gelatinous exudate, which on direct bacterial examination shows many organisms with enormous capsules. We hesitate to consider this infection an epizootic disease analogous to that caused in guinea pigs by Group C *hemolytic streptococci* (20, 21) because we think that the infection is generally initiated by biting.

in a dilution of 10^{-6} when titrated intracerebrally in mice. The spleen from 1 of the guinea pigs inoculated with a suspension of feces likewise possessed the soluble antigen of choriomeningitis; in addition, bacteriologically sterile blood drawn from another sick animal on the 9th day after receiving fecal material produced a fatal infection when injected into 2 normal guinea pigs but caused no illness in 2 guinea pigs known to be immune to choriomeningitis virus.

The results of the experiment indicate that the virus of lymphocytic choriomeningitis appears in the urine and feces of infected hamsters in amounts comparable to that found in the blood.

Comparatively minor pathological changes were generally observed in hamsters affected by this silent virus infection. The only macroscopic abnormality regularly encountered was a moderate enlargement and congestion of the spleen. Microscopic examination of sections from various organs revealed few changes worthy of note. Histological sections prepared from brains which had been demonstrated by titration studies to contain virus in appreciable amounts generally showed only a mild meningeal reaction consisting of a few scattered lymphocytes in the subarachnoid space. This was true even of hamster, 1-15, which appeared moribund on the 22nd day. On the other hand, hamster, 1-12, which was moribund on the 28th day, was found to have an extensive meningo-encephalitis and pyelonephritis on histological examination. Bacteriological cultures of the brain and spleen of the latter animal were sterile, but those of the liver revealed a few colonies of *Klebsiella capsulata*. The lesions in the brain of this hamster consisted of collections of mononuclear cells about vessels in the meninges and brain tissue, and swelling and hyperplasia of cells of the choroid with scattered infiltrations of lymphocytes about the capillaries; destruction of nerve cells was not encountered.

Failure to Obtain the Virus of Choriomeningitis during Serial Passage of "Normal" Hamster Tissue

Inasmuch as epizootics of lymphocytic choriomeningitis (24) have been observed in laboratory stocks of white mice, monkeys, and guinea pigs, the question arose as to whether or not the virus occurred as a silent infection in our so called normal hamsters. During the course of the present work, experiments designed to test the susceptibility of hamsters to the virus of measles were carried out; evidence was obtained which indicated that the virus of choriomeningitis was not present fortuitously in this host, as shown by the following experiments.

Blood and throat washings were obtained from 3 children within a few hours after the first appearance of a measles rash.[2] Four hamsters were inoculated intranasally,

[2] We wish to thank Dr. Jerome Cohn and Dr. Irving Klein for making available to us material from two of these children who were patients in the Willard Parker Hospital, New York. The third individual was a patient in The Rockefeller Hospital.

intracerebrally, and intraperitoneally with plasma from patient, E. H., and 4 were injected intracerebrally, intranasally, and intraperitoneally with ether-treated throat washings. None of the animals developed evidence of disease except one of the hamsters that received plasma; it was ill on the 5th day and when sacrificed at that time was found to have pulmonary consolidation which yielded a heavy growth of *Klebsiella capsulata*. This organism induced a fatal, generalized infection in normal hamsters. A suspension of pooled brain and lung tissue obtained from one of the original hamsters on the 7th day following injection with the patient's plasma was bacteriologically sterile and was passed to normal hamsters. In this manner 4 serial transfers were made. None of the animals showed clinical signs of disease. Moreover, no significant lesions were observed in those which were sacrificed for passage. Serum taken from the hamsters 3 to 4 weeks after injection with human or with hamster-passaged materials did not contain complement-fixing antibodies for the soluble antigen of choriomeningitis, and, in addition, serum from several hamsters gave negative results for neutralizing antibodies of choriomeningitis. Materials from patients, L. A. and H. G., were studied in a similar but less thorough manner. Eight hamsters were injected with plasma and throat washings from the former patient and a subsequent passage was made, while only 4 animals were inoculated with serum from the latter patient. All of the animals remained well and none of them developed antibodies specific for choriomeningitis.

Among the 34 hamsters from our normal stock employed in these experiments there was no evidence of an indigenous infection with the virus of lymphocytic choriomeningitis.

Correlation of Virus, Soluble Antigen, and Antibodies in the Syrian Hamster

Tissues of hamsters infected with the virus of choriomeningitis contain a specific soluble antigen which is serologically identical with that found in tissues of other animals affected by the disease (25). The antigen has been consistently demonstrable in complement-fixation titers of 1:8 to 1:32 in preparations of spleens taken from hamsters 5 to 8 days after injection of virus. It is no longer detectable, however, by the 14th day which is approximately the time when complement-fixing antibody makes its appearance in the circulating blood (see Table I). The complement-fixing antibody increases in amounts until about the 4th to 6th week; it then gradually declines but persists, in some instances, for at least 8 months.

It is apparent from the data presented in Table I that complement-fixing antibody is present in appreciable amounts at a time when virus is circulating in the blood. Moreover, the disappearance of circulating virus after the 3rd week seems to bear no direct relationship to the general increase at about this time of antisoluble substance antibody. For example, both blood and organs of hamsters, 5-12 and 5-15, which were sacrificed on the 21st day, contained 10^3 M.L.D. of virus and the complement-fixing titer of their pooled serum was 1:32, whereas hamster, 5-17, sacrificed on the 28th day, had no demonstrable

virus in its blood or organs and the complement-fixing titer of its serum was also 1:32.

The data summarized in Table I indicate that the blood and splenic tissue frequently lose their infectivity by the 28th day, but occasionally small amounts of circulating virus may persist until the 35th day. In addition, the data show that neutralizing antibodies generally appear in the serum at about the 6th week. It may be pointed out that in 3 animals, which were sacrificed at 5, 6, and 8 weeks after inoculation, virus was demonstrable in the brain but not elsewhere. Moreover, 2 of these animals, 1-2A and 1-3, possessed neutralizing antibody in their blood at a time when active virus was obtained from their brains. In general, these observations indicate that resistance to infection becomes evident during the 4th week after inoculation when virus begins to disappear from the blood and most of the organs and at a time when neutralizing antibodies are not present in quantities sufficient to neutralize 1000 M.L.D. of virus; by the 6th week, however, such an amount of neutralizing substance has appeared in the serum of the majority of the animals.

Simultaneous Infection of the Hamster with the Viruses of Lymphocytic Choriomeningitis and St. Louis Encephalitis

The virus of choriomeningitis has inadvertently been carried along with other viruses during serial passage; *e.g.*, with distemper virus transmitted in dogs (26) and with rabies virus grown in tissue cultures (27). Armstrong (28) has shown that a known mixture of the viruses of choriomeningitis and St. Louis encephalitis passed serially in monkeys results in the loss of the latter agent. On the other hand, when a similar mixture of the two agents is transmitted in mice, the virus of choriomeningitis is lost after a few passages while that of St. Louis encephalitis is maintained. Since the virus of choriomeningitis as a rule produces a generalized, non-lethal infection in the hamster at a time when infection with the virus of St. Louis encephalitis (1, 2) is causing death, it seemed likely that serial transmission of both agents might be accomplished simultaneously in this host. The results of an experiment designed to test this possibility are presented below.

A mixture containing equal parts of a 10 per cent suspension of guinea pig brain infected with the W.E. strain of the virus of choriomeningitis and a 10 per cent suspension of hamster brain infected with the Hubbard strain of the virus of St. Louis encephalitis was inoculated intracerebrally into 2 hamsters. The animals became moribund on the 4th day and were sacrificed. Their brains were removed and pooled, and a suspension of them was passed to normal hamsters. In such a way 5 successive passages were made. Organs from a hamster of the 5th passage (LCM + St.L. 5-1) which died on the 4th day after inoculation were tested for the presence of the two viruses in the following manner.

Suspensions prepared from brain, lung, and spleen were titered in duplicate in

groups of normal mice and of mice immune to choriomeningitis; in addition, the suspension of brain tissue was titered intracerebrally in normal guinea pigs. The choriomeningitis immune mice were approximately 7 weeks old when used and had survived intraperitoneal injections of 100 and 10,000 M.L.D. of active virus at the age of 3 and 6 weeks, respectively. A control group of the immune animals resisted 10^5 lethal intracerebral doses of the potent, W.E. guinea pig strain of virus. The results of the titration of tissues from hamster, 5-1, are summarized in Table II.

TABLE II

Simultaneous Passage in Hamsters of the Viruses of Lymphocytic Choriomeningitis and St. Louis Encephalitis

Inoculum from hamster, 5-1	Test animals	Dilution of intracerebral inoculum							
		10^{-1}	10^{-2}	10^{-3}	10^{-4}	10^{-5}	10^{-6}	10^{-7}	10^{-8}
Brain	Normal guinea pigs	2/2	2/2	2/2*‡	2/2	2/2	2/2	2/2	0/2
	LCM immune mice	3/3	3/3	3/3	3/3	3/3	3/3§	2/3	
	Normal mice	3/3	3/3	3/3	3/3	3/3	3/3	2/3	
Lung	LCM immune mice	2/3	2/3	1/3					
	Normal mice	3/3	2/3	0/3	0/3	0/3	0/3	0/3	0/3
Spleen	LCM immune mice	0/3	0/3	0/3					
	Normal mice	3/3	3/3	1/3	0/3	0/3	0/3	0/3	0/3

Numerator represents number of animals which survived; denominator the number of animals inoculated.

* A 10^{-3} dilution of brain tissue of 1 of these guinea pigs when inoculated into 2 normal guinea pigs caused the death of both and when inoculated into 2 LCM immune guinea pigs produced no illness.

‡ Spleens from both these guinea pigs contained the specific soluble antigen of choriomeningitis.

§ A 10^{-3} dilution of pooled brains from these mice killed 2 LCM immune hamsters but did not affect 2 St. Louis immune hamsters.

The data presented in Table II indicate that both viruses were present in large amounts in the brain of hamster (LCM + St.L.), 5-1. The titration end point of 10^{-7} obtained in the normal and choriomeningitis immune mice warranted the assumption that encephalitis virus was present. This was conclusively proved by the intracerebral inoculation of a 10^{-3} dilution of brain tissue from one of the moribund choriomeningitis immune titration mice into 2 hamsters immune to St. Louis encephalitis and into 2 hamsters immune to choriomeningitis. The former animals survived without obvious illness while the latter died on the 4th and 5th days after inoculation. Since guinea pigs

are highly susceptible to the virus of lymphocytic choriomeningitis (4, 16) and relatively insusceptible to the virus of St. Louis encephalitis (29), the results of the titration of the hamster brain (5-1) in this species suggested that the virus of choriomeningitis was present. Indeed, the presence of choriomeningitis in 2 of the guinea pigs employed in the titration was subsequently established by the demonstration of the presence of the soluble antigen of choriomeningitis in extracts prepared from their spleens (complement-fixing titer of each, 1:16); moreover, a 10^{-3} dilution of brain tissue from one of the titration guinea pigs killed 2 normal guinea pigs but did not affect either of 2 choriomeningitis immune guinea pigs injected at the same time. Titration of partially consolidated lung tissue of hamster, 5-1, indicated that a small amount of encephalitis virus was present since the end points were similar in normal and in choriomeningitis immune mice. On the other hand, the spleen of this hamster apparently contained only the virus of choriomeningitis. Further identification of the agents in lung and spleen was not attempted. It thus appears that once the virus of St. Louis encephalitis has been contaminated with the virus of choriomeningitis, both agents can be transmitted serially in hamsters by the intracerebral route for at least 5 transfers. Furthermore, the clinical disease and the pathological lesions[3] produced by the mixed virus infection are indistinguishable from that produced by the virus of encephalitis alone.

DISCUSSION

The virus of lymphocytic choriomeningitis multiplies readily in the adult Syrian hamster, producing a systemic disease in which large amounts of virus are demonstrable in the blood, organs, urine, and feces. Infection in these animals is rarely accompanied by obvious signs of illness; furthermore, significant histopathological lesions are only occasionally encountered in their brains or elsewhere. Antibodies for the soluble antigen of choriomeningitis are demonstrable in the serum during the 2nd week, at a time when virus is still present in high titer in blood and organs. This observation provides further evidence for the opinion (19) that antisoluble substance antibodies possess little if any power to neutralize the virus. Although neutralizing antibodies are not detectable by our method until 6 weeks after inoculation, the earlier

[3] The pathological changes observed in brains of hamsters injected intracerebrally with the virus of St. Louis encephalitis are similar to those seen in infected mice (30). Meningeal infiltrations of mononuclear cells, particularly about vessels, are common; perivascular cuffs containing the same type of cells are found throughout the brain tissue; degeneration of nerve cells occurs here and there in all areas but is more frequent in Ammon's horn. Involvement of the choroid is not prominent in hamsters infected with the virus of encephalitis and it is not outstanding in those with choriomeningitis.

appearance of small amounts of these substances may account for the loss of infectivity of blood and most organs during the 4th week of the disease. The simultaneous presence of appreciable quantities of virus in the brain and of neutralizing antibody in the serum was demonstrated in 2 animals, one in the 6th and another in the 8th week. This observation suggests that the virus may parasitize certain cells for long periods of time without destroying them and without being itself destroyed by them. The inability of neutralizing antibody to penetrate intact cells and to inactivate virus situated intracellularly is well established (31).

Silent infection with the virus of choriomeningitis occurs in animals other than hamsters. For example, mice contaminated *in utero* present little evidence of disease; nevertheless, their blood, urine, and nasal secretions may be infectious for months (22). Moreover, certain strains of the agent produce in guinea pigs a systemic disease which is manifest clinically only by a slight rise in temperature of a few days' duration (25, 32). It should be pointed out that disease of a severity intermediate between the lethal type caused by the W.E. strain and the almost inapparent type caused by the W.W.S. strain can be produced in guinea pigs by still other strains of virus (25). Therefore, silent infections with this virus appear to represent only one of a series of stages of severity. Thus, the response of dogs and ferrets (26) might be considered to belong on the scale close to the inapparent infections, because in these animals choriomeningitis virus multiplies sufficiently to be transmitted through at least several serial passages when distemper virus is carried concurrently. Finally, it is necessary to reconsider the group of animals (19) which have been regarded as resistant to the virus of choriomeningitis but which develop specific antibodies following inoculation of the virus. Can these antibodies be considered to develop entirely in response to a relatively small amount of virus which does not multiply? It seems unlikely that a single intraperitoneal injection of active virus would be sufficient to induce the formation of complement-fixing antibodies in rabbits (19) if no multiplication of virus had occurred. Although rabbits are considered resistant to choriomeningitis, the intracerebral inoculation of very young animals may be followed by retardation of growth and by the development of mild lesions in the choroid plexus and meninges (19). This at least suggests that some multiplication of virus occurs in rabbits and leads one to wonder whether or not a similar phenomenon occurs in other so called resistant animals which form specific antibodies.

SUMMARY

The virus of lymphocytic choriomeningitis produces an intense systemic infection in Syrian hamsters with few if any clinical and pathological signs of disease. Specific soluble antigen is demonstrable in the spleen of infected animals until about the 14th day when antisoluble substance antibodies make their appearance. Circulating virus disappears after the 4th week and neu-

tralizing antibodies are present in serum in detectable amounts shortly thereafter; both types of antibody persist for at least several months.

The viruses of St. Louis encephalitis and lymphocytic choriomeningitis can be concurrently passed in series in the brains of hamsters. The resultant disease is indistinguishable from that caused by the virus of St. Louis encephalitis alone.

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