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Variations in Pathways by Which Equine Encephalomyelitic Viruses Invade the CNS of Mice and Guinea-pigs.

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Eastern equine encephalomyelitic (E.E.E.) virus, injected into the leg muscles of 15- to 21-day-old mice, invades the central nervous system (CNS) along the local peripheral nerves in only about 5% of the animals, while in most of the others it appears to be eliminated from the blood onto the olfactory mucosa, invading the CNS by the olfactory pathway, and when that pathway is blocked by preliminary chemical treatment of the nasal mucosa most, but not all, of the animals escape CNS involvement.[1] Further study by the method of partial serial sections of the entire CNS[2] revealed that when mice, given the virus intranasally, succumb in spite of the chemical treatment, the lesions are still distributed along the olfactory pathways and connections, showing that the treatment did not provide a complete barrier. When, however, mice receiving the virus *intramuscularly* succumb in spite of chemical blockade of the olfactory pathway, the localization of lesions indicates that the CNS was invaded by other pathways, the following types having been encountered: (a) lesions limited to the spinal cord and medulla, indicative of spread *via* the nerves supplying the inoculated muscle; (b) lesions involving chiefly the cochlear ganglion of one side and the inferior colliculus and medial geniculate body of the opposite side (*i.e.*, a unilateral involvement of the auditory pathway and its central connections); and (c) lesions limited to a focus in the vicinity of the medullary nucleus of the 7th nerve. Hence, these and other pathways may occasionally be utilized by virus injected into the leg muscles (and also intraäbdominally) of normal mice as well as of those with chemical blockade of the olfactory pathway. In one normal young mouse injected intraäbdominally with E.E.E. virus both the auditory and vestibular pathways appeared to be involved. It is remarkable, however, that in these mice the localization of lesions practically always corresponded to some definite pathway, suggesting that the virus was set free in one focus from

1 Sabin, A. B., and Olitsky, P. K., *Am. J. Path.*, 1937, **13**, 615.

2 Sabin, A. B., and Olitsky, P. K., *J. Exp. Med.*, 1938, **67**, 201; Sabin, A. B., PROC. SOC. EXP. BIOL. AND MED., 1938, **38**, 270.

which it spread along the nervous pathways connected with it (excepting the olfactory pathway, there is as yet no evidence to indicate whether that focus is within or outside the CNS) rather than liberated indiscriminately throughout the CNS.

A study of the localization of lesions in normal guinea pigs which were given mouse-passage E.E.E. virus into the leg muscles revealed, however, this diffuse distribution of lesions yielding a picture which in its totality has not hitherto been encountered in mice. The most striking difference is in the involvement of the neopallial cortex which in the mouse only rarely shows lesions and then only as limited foci bearing some relationship to an affected pathway, while in the guinea pig there are numerous lesions which are diffusely scattered, bearing a relationship only to the blood vessels which themselves show evidence of injury. These perivascular lesions frequently consist of almost complete neuronal necrosis with an abundant infiltration of polymorphonuclear leucocytes, while in many instances large numbers of polymorphonuclear leucocytes are present around the vessels without any evidence of neuronal necrosis. This diffuse, perivascular, neuronal necrosis in the guinea pig's neopallial cortex corresponds so closely to the type of lesion produced by toxoplasma[3] growing through the vessels in the brains of mice, that it strongly suggests that in the guinea pig E.E.E. virus also grows through the vessels and involves the nerve cells around them, a possibility already considered by Hurst[4] on experimental grounds. In addition there is usually sufficient neuronal necrosis along definite parts of the central olfactory connections to suggest that progression also occurred along this pathway. In only one instance was there flaccid paralysis of the posterior extremities following inoculation of the virus into the leg muscles (the only instance with extensive involvement of the spinal cord) but even in this animal there were concomitant signs of encephalitis with widely scattered lesions in the neopallial cortex.

With *Western* mouse-passage equine encephalomyelitis virus (W.E.E.) a somewhat different course was observed following intramuscular injection in both mice and guinea pigs. Among 15-day-old mice, 80 to 90% of the animals exhibit only signs of encephalitis (pathology indicative of invasion along olfactory or other pathways without evidence of either diffuse hemato-encephalic spread or progression *via* the local nerves), and only 10 to 20%, signs of flaccid paralysis (with pathological evidence of spread only

[3] Sabin, A. B., and Olitsky, P. K., *Science*, 1937, **85**, 336.

[4] Hurst, E. W., *J. Path. and Bact.*, 1936, **42**, 271.

by way of the local peripheral nerves). Among 21-day-old mice, however, 70 to 80% develop flaccid paralysis, 10 to 20% exhibit only signs of encephalitis, and the few remaining ones show no evidence of CNS disease. About half the number of 7- to 10-day-old guinea pigs injected into the leg muscles with the mouse-passage strain of W.E.E. exhibit only signs of encephalitis; an occasional young animal shows no nervous signs at all but most of the others reveal flaccid paralysis of the posterior extremities (first on the inoculated side) with pathological evidence of spread only along the local peripheral nerves and none of the diffuse vascular and perivascular lesions in the neopallial cortex. Since the capacity to produce such a high incidence of flaccid paralysis following injection into the leg muscles has not been noted previously in work on W.E.E., it is not improbable that it may be related to the number of mouse passages our strain of virus has undergone.

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Age of Host and Capacity of Equine Encephalomyelitic Viruses to Invade the CNS.

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Studies on the nature of various types of natural resistance to viruses affecting the central nervous system (CNS) have already disclosed that as mice and guinea pigs grow older there appear certain localized barriers in the peripheral and central nervous systems which, because of the nature of neural progression of peripherally injected vesicular-stomatitis virus, are capable of preventing it from invading the CNS or from spreading beyond a certain point, depending upon the route of inoculation.[1] Still another type of change that occurs with age was revealed in the course of investigations on the manner in which the viruses of equine encephalomyelitis (E.E.) invade the CNS after inoculation into the muscles of an extremity. This change which appears to involve the blood vessels, which the E.E. viruses must traverse or grow through in order to invade the CNS,[2, 3, 4] is the subject of the present report.

[1] Sabin, A. B., and Olitsky, P. K., *J. Exp. Med.*, 1937, **66**, 15, 35; 1938, **67**, 201, 229.

[2] Sabin, A. B., and Olitsky, P. K., *Am. J. Path.*, 1937, **13**, 615.

[3] Sabin, A. B., and Olitsky, P. K., PROC. SOC. EXP. BIOL. AND MED., this issue.

[4] Hurst, E. W., *J. Path. and Bact.*, 1936, **42**, 271.