CHAPTER I

INTRODUCTION

Epidemiology of Rabies.

Infection with the rabies virus, has been a dreaded disease throughout recorded history. It was recognized in the ancient civilizations of Egypt, Greece and Rome (1).

Human rabies is one of the most severe of all communicable diseases. World wide, a total of about 1,000 fatal cases are reported annually to the WHO and the actual number must be considerably more.

Unlike smallpox, rabies has an extensive, uncontrollable, sylvan reservoir, comprising such animals as bats, coyotes, foxes, jackals, mongooses, skunks, and weasels, so there is no possibility of control by the mass vaccination of animals. Further, in Thailand, the reluctance to destroy "street-dogs", many of which become rabid, aggravates the problem. Approximately more than 300 cases of rabies are reported every year in Thailand (2).

Saliva containing virus, introduced into humans, by the bite of a rabid animal, is the most usual means of transmission, although infection via scratches or the respiratory tract have also been reported. Bats produce infectious aerosols and domestic

pets frequently lick their owners.

The virus responsible for the disease is known as "street virus", (virus de rage de rue). This virus passaged fifty times, intracerebrally in rabbits, is known as "fixed virus", (virus fixe). However, the attenuation is only partial, since "fixed virus" is still pathogenic for humans and animals.

Properties of Rabies Virus.

Rabies is a rhabdovirus, its virions are bullet shaped, having one rounded and the other planar end. Regularly shaped projections cover the surface, each with a knob like structure at its distal end. The helical nucleocapsid, 18 nm. in width, consists of one molecule of single stranded RNA, of negative polarity, many identical copies of N protein (69,000 d) and a few copies of the RNA dependent, RNA transcriptase (3).

The viral envelope consists of a lipid bilayer and the external projections are glycoprotein (G protein, 8,000 d). Two matrix proteins, which are not glycosylated, M1 (40,000 d) and M2 (25,000 d), reinforce the envelope internally. The glycoprotein projections, which also act as hemagglutinins to goose erythrocytes, attach the virion to host cell receptors.

Serology.

Up until the time that rabies was recognized as a member of the Lyssavirus genus, it was thought to be a single antigenic "species". Now however, it has been grouped with several

serologically related viruses, two from Nigeria, the Lagos bat virus, isolated in 1958 from Eidolon helvam (4), the Mokola virus, isolated in 1968 from a shrew (5), and another from South Africa, the Duvenhage virus, isolated from a human in 1970, who died following a bite from a bat (6).

Other related species are the Obodhiang virus, isolated from mosquitoes in the Sudan (7) and the Kotonkan virus isolated from a species of ridges in Nigeria (8). The Nigerian horse virus, also produces a disease resembling rabies(9).

Complement fixation assays have indicated close antigenic similarity between the Lyssaviruses, although only limited cross-reactivity can be shown by viral neutralization (10).

Pathogenesis of Rabies Infection.

Following the isolation of "street virus" from the saliva of rabid dogs by Louis Pasteur, he injected it into the brains of rabbits. The rabbits eventually became paralysed and died within 2-3 weeks.

After several such passages, the "fixed virus" had somewhat changed characteristics. It failed to infect animals unless injected directly into the brain and when administered by other parenteral routes, it could protect laboratory animals against a subsequent challenge with virulent "street virus".

The clinical manifestations of rabies infection are very similar in both dog and human. The site and depth of bite are

crucial factors in determining the degree of penetration of the virus and its rate of spread, and hence, the rapidity of the onset of infection.

The virus multiply in the infected host and progress along the nerves reaching the central nervous system (CNS). Here they propagate in the area of the spinal or dorsal root ganglia, brain stem and cerebrum and then can be passed to other organs, such as the salivary glands, skin, hair follicles and corneal cells (11).

Observations in the human and the dog have divided the disease into two distinct categories. The encephalitic or furious form, and the paralytic or dumb form (1, 12). At the present, it is not possible to determine whether the very obvious differences in these two manifestations of the disease are due to differences in the immune responses of the host or in the pathogenesis of the infection itself.

Iwasaki (13), Smith (14) and Tignor (15) have each discussed the role of the immune response in the development of the disease. Immunosuppressed mice take longer to succumb to rabies infection than do immunocompetent mice. Further the onset of paralysis following transient immunosuppression, is related, temporally, to a return to immune responsiveness. The "early death" phenomenon (13, 14, 15, 16) has been observed in humans exhibiting a positive immune response involvement, particularly when associated with a prior immunization.

The actual distribution of the virus within the nervous tissue, also appears to play a role in the occurrence of paralytic rabies, as suggested by Chopra (17) and Sheahan (18). Comparing hosts with the symptoms of paralysis and encephalitis, fewer inclusion bodies were found in the cerebral cortex in the paralytic, than in the encephalitic form. Also inflammatory reactions appeared to be generally confined to the spinal regions in paralytic rabies rather than to the cerebral cortex.

Further, an ascending wave of rabies infection of the CNS, shortly precedes the onset of paralysis (19). Johnson (20) noted that rabies virus appeared to selectively damage the limbic system while sparing neocortex during the early stages of the disease. This observation correlates with the clinical symptoms. So, the distribution of the virus within the nervous system, may well predicate the clinical manifestations of rabies infection.

Since previous studies on human paralytic (17) and encephalitic (21) rabies have not been attempted to assess the relevance of viral distribution, except for the presence of inclusion bodies on such pathogenesis, we are attempting, in this study, to expose any correlation between the distribution of virus and its specific clinical manifestations. We shall concentrate particularly, on the early stages of infection, before the virus becomes widely distributed in nervous tissue. Our studies will investigate both the paralytic and encephalitic modes.

Examining the early stages of infection, we expect to be

able to demonstrate an abundance of the virus in the spinal cord in the paralytic form, compared to a large preponderance of the virus in the brain in the encephalitic form. The presence of the virus will be defined and quantitated in neurons and non-neuron cells by the immunohistochemical technique of peroxidase staining.

Although the major purpose of this study is to define the distribution of rabies virus in the nervous system of human patients afflicted with either paralytic or encephalitic rabies, we rarely encounter human sufferers, except those who are in the terminal stage of the disease. Therefore data obtained from study in human might only reveal a uniform distribution of antigen in every central nervous system regions. So, we shall make these studies in rabid dogs, when we can readily study the early stages of the disease, confident that we can extrapolate our findings to the human situation.