EFFECT OF HERPES SIMPLEX VIRUS ON THE EYE AND ITS MANAGEMENT.

THESIS..

Submitted for Partial Fulfilment of Master Degree of Ophthalmology.

BY

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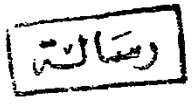
SUPERVISOR



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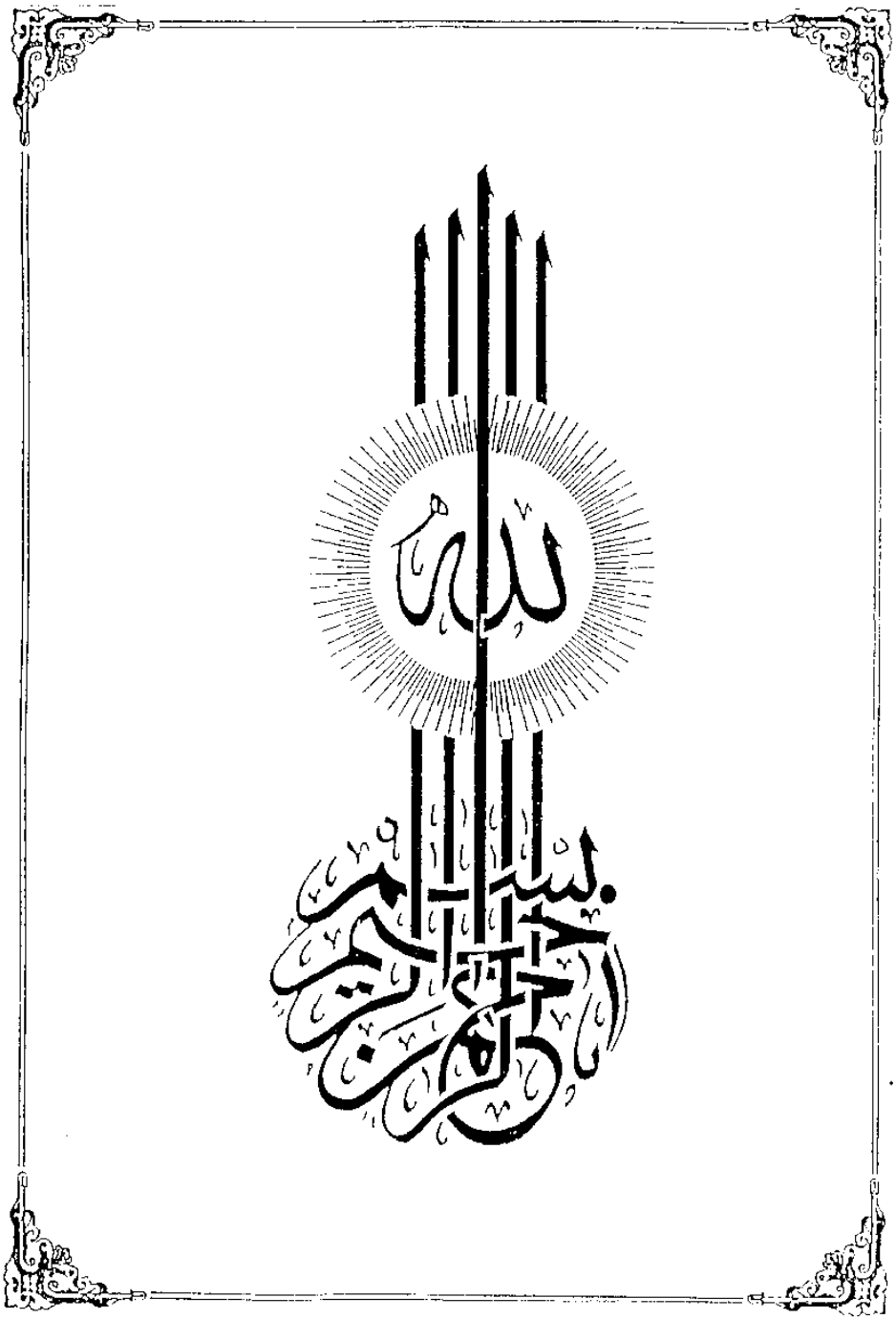

A C K N O W L E D G E M E N T

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I N T R O D U C T I O N

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Herpes simplex virus (HSV) or herpes simplex hominis is one of the herpesviruses which can affect man. Primary infection of HSV occurs early in life and is often asymptomatic. Antibodies develop, but the virus is not eliminated from the body and a carrier state develops. HSV infections recur in some individuals and do not in others. HSV can cause acute gingivostomatitis, eczyma herpeticum, herpes labialis, genital herpes, encephalitis, and other clinical pictures. HSV can affect the eye in primary or recurrent forms. It gives manifestations in the eyelid, the conjunctiva, the cornea, the uveal tract, and the retina. Herpes simplex keratitis is a common cause of corneal opacities and subsequent visual disability, so herpes simplex infection of the eye requires prompt treatment.

HERPES SIMPLEX VIRUS

Morphology of herpes simplex virus (HSV)

HSV is a large deoxy-ribo-nucleic acid (DNA) virus. The three main components of HSV are : (1) electron dense DNA-rich core surrounded by (2) multilayered icosahedral capsid consisting of 162 capsomeres enclosed in (3) ether-sensetive envelope of glycoprotein and lipid. These components together constitute the infectious extracellular form of the virus, which is spherical in shape and measures approximately 1800 A° in diameter. The virus is an obligate intracellular parasite with a linear double stranded DNA genome of 90 to 100 x 10^6 daltons in molecular weight. (Wildy et al., 1960) (Fig. 1).

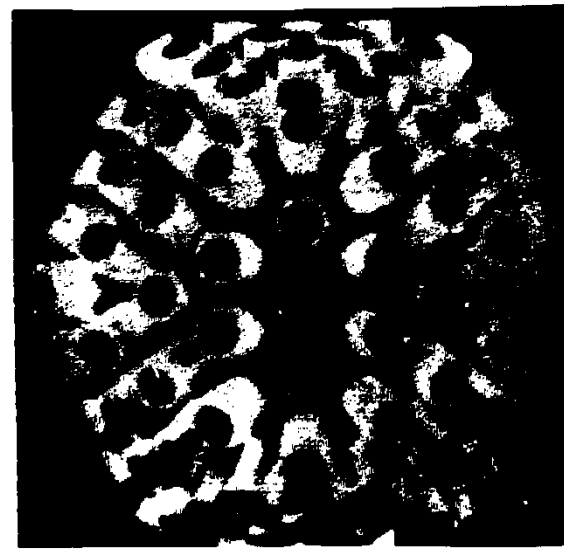

Fig. 1: Herpes simplex virus (Duke Elder, 1965).

Virus replication

The life cycle of HSV, which is illustrated in fig. 2 , is initiated when the virus:

(1) comes into contact with a susceptible host cell to which it is bound by an electrostatic forces (coster, 1978).

(2) The virus enters through cell membranes. Enteranc is affected by the ionic state of extracellular fluid. Perhaps the virus particles compete with large anions for a limited number of receptor sites. Two mechanisms are known for cell penetration which are pinocytosis;and fusion of the lipoprotein envelope of the virus with cell membrane (Dales and Silverberg, 1969). It appears that viral genetic material can pass from cell to cell in the absence of demonstrable virus particles. (Stoker, 1958). The infection of cells is inhibited by addition of polyaniomic compounds such as heparin sulfate to the medium, even in small amounts. The highly negative charge of heparin may prevent the attachment of virus to the cell (Vaheri and Cantell, 1963).

(3) After entering the cytoplasm of the infected cell, the outer lipoprotein envelope is removed and the

remaining DNA protein complex passes into the nucleus where replication of DNA and transcription of messenger ribonucleic acid (mRNA) occurs. mRNA is passed into the free and membrane- bound polyribosomes where it acts as the template for the translation of early proteins, which are translated from viral RNA transcripted before the replication of viral DNA. Early proteins represent the minority of virus- coded proteins produced in infected cells and are mainly enzymes and proteins which seem to have a role in shutting down most protein synthesis. Late proteins are mainly structural proteins for the virion, they pass back into the nucleus for assembly into virions. (Coster, 1978).

(4) Maturation of the virus occurs by formation of envelope formed from the inner lamella of the host nuclear membrane. This altered nuclear membrane enfoldes the virus nucleocapsid as it passes through it to the cytoplasm (Honess and Roizman 1974).

The products of the replicating genome are :

- Structural proteins of the virion.
- Enzymes for protein synthesis.

- Regulatory proteins capable of suppressing most of protein synthesis.
- Membrane proteins.

The production of enzymes and proteins incorporated in the membrane of infected cells as antigens is important in the development of the pathology of herpetic keratitis. Viral enzymes alter the cellular biochemistry. Of these enzymes are: DNA polymerase which is suppressed by Adenine arabinoside and, thymidine kinase. These enzymes are coded from viral genome and are not induced by the host. Thymidine kinase is involved at one step of the phosphorylation of thymidine to deoxythimidine triphosphate. Both 5 - iodo - 2 deoxyuridine and trifluorothymidine inhibit this enzyme and have an additional suppressive effect on virus replication by substituting thymidine in DNA. Viral cycle takes about 6 hours (Coster, 1978).

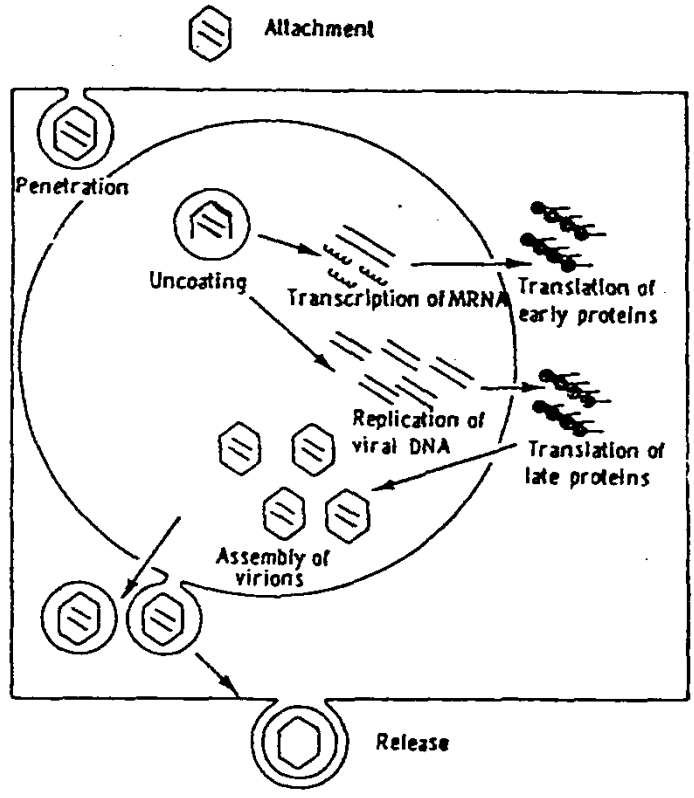

Fig. 2: Diagram of multiplication cycle of H.S.V. (Coster, 1978. Quoted from Fenner and White, 1976).

Viral cytopathic effect

Cells may respond to viral infection with (1) productive infection in which the cytopathological effect is maximal and large numbers of virus particles are produced. This occurs commonly in epithelial cells which account for ulcerative nature of infection, or (2) with non productive infection. In this type the cells harbour and replicate viral genetic material, but are not destroyed (Nahmias and Roizman 1973). Mesodermal and neural cells are more prone to non productive infection which may account for immune response in producing stromal lesions and for the role of corneal nerves and their central connections in the development of latency and recurrence (Coster,1978).

The productive infection of cells with HSV results in a gross metabolic disturbance and the cell is entirely devoted to virus replication. There is an accumulation of macromolecules which may be toxic to the cell. The infected cells swell and exhibit an alteration in transmembrane potentials with leakage of macromolecules(Coster, 1978). Infected cells exhibit a tendency to aggragate or even fuse with other infected cells (Roizman,1971) while retaining a normal or decreased adherence to non infected cells. This phenomenon is used clinically in minimal wipe debridement.

Virus isolation and culture

Specimens for HSV isolation may be collected from the lid, conjuctival or corneal lesions. After appropriate local anaesthesia, conjunctival specimens are taken by firmly rubbing the everted conjunctiva with a dry cotton swab. Material from the lid lesions may be collected with a cotton swab after pricking the centre of the ulcer or vesicle with a fine needle. Specimens from corneal ulcers may be taken with a dry cotton swab by gently rubbing the marginal area of the lesion. All material for HSV isolation should be placed in a suitable transport medium and sent immediately to the laboratory. When immediate isolation can not be carried out, specimens should be frozen at - 70°C or -180°C in a liquid nitrogen refrigerator (Gordon et al., 1969).

Whitcher et al.(1976) in their study collected corneal specimens either by rolling a sterile cotton - tipped applicator gentely over the affected cornea or by removing all of the loose epithelium around the lesion with a cotton - tipped applicator. They placed the applicator in a sterile silicone tube containing 1 ml of Eagle minimum essential medium, supplemented by 5% fetal calf serum with penicillin