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Cytopathology in Viral Diseases

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Editor's Preface

This Monograph offers a concise survey of the cytopathology of viral diseases of vertebrates as observed *in vivo*, and of the mechanisms influencing the cytopathic effects of viral infections, particularly at the ultrastructural level. Since the author's primary research concerns animal diseases, the focus of the volume is upon viral infections of lower vertebrates, with human diseases viewed in a comparative sense. The book is organized in terms of virus families and groupings. Along with textual summaries describing the cytopathology produced by each group and subgroup, numerous fine microscopic and electron microscopic illustrations are included, providing a very useful reference resource for the student of viral cytopathology.

JOSEPH L. MELNICK

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Introduction

Viral diseases of the vertebrate animal species are characterized by distinctive cytopathic alterations in tissue systems of the host. In this monograph, those changes are differentiated with an attempt to interpret pathogenetic features that groups of viruses appear to have in common. The paravaccinia viruses, the rinderpest-measles-canine distemper group and the non-arthropod-borne togaviruses, once revealed to be related antigenically, have been shown to cause remarkably similar infectious patterns and changes in cellular ultrastructure.

Viruses induce cytopathic alterations by disrupting cellular structures both selectively and nonspecifically. A cell membrane may be destroyed directly by replication of the virion within the membrane or indirectly by the destruction of an organelle upon which the membrane depends for its integrity. In the early synthetic phases of infection, viral-induced depletion or shutdown of required enzyme systems in the host cell are the most obvious and significant factors that affect cellular viability. The protein-synthesizing organelles are injured and, characteristically, small foci of *lysis* develop in the karyoplasm or cytoplasmic matrix at the site where uncoating of the viral genome has occurred or where synthesis of viral mRNA has been initiated. Proteins and lipoprotein membranes redistribute, disintegrate and disappear. Disturbed protein synthesis is most often reflected in the destruction of rough endoplasmic reticulum which progressively shows detachment of ribosomes, fragmentation, and vesiculation. Within these 'cleared' foci arise the precursors of the virion. As infection proceeds, these subtle changes progress to overt cytopathology.

In later synthetic phases, the production and accumulation of viral proteins results in paralysis of cellular function. The normal pathways of cellular, exocytotic protein secretion do not function and masses of viral-induced proteins and excess components of virions accumulate as inclusion bodies which distort the cell. In the process of destruction of internal cellular organelles, the transport mechanisms of the plasma membrane are secondarily depressed and cell swelling develops. Injury to the host cell plasma membrane

may also occur by the replication of the virions within the plasma membrane itself or as immunologic destruction brought about by attachment of antibody or plasmacytes to the sites of viral antigens on the cell surface.

Cell swelling is a fundamental expression of viral-induced injury. It occurs when the altered plasma membrane allows excessive water uptake and accumulation. Injury to the ATP-requiring mechanisms of active transport of sodium and water within the plasma membrane lead to overhydration, cytoplasmic swelling, and lysis. Water may expand the cytoplasmic matrix as it does in poxviral infections or may accumulate selectively within organelles such as mitochondria, Golgi complex or cytocavitary network. In the latter case, organelles become markedly dilated with water in a pattern of cellular degeneration called vacuolar degeneration. In either case, cell swelling is characterized by enormous expansion of cell volume, dilution of cytoplasmic structures, and the dispersal of ribosomes and cytocavitary network. The end result includes the loss of specialized surface structures (cilia, microvilli, junctional complexes) and an exaggeration of cytoplasmic ecdysis – the formation of cytoplasmic blebs at the cell surface and their detachment from the cell.

Lysosomes play a prominent role in most viral-induced cytopathic changes. *Autophagy* (autophagocytosis) is the usual reaction in cells injured sublethally by viruses. Sometimes referred to as 'intracellular phagocytosis', autophagy is characterized by the sequestration of portions of the cytoplasmic matrix and its organelles into membrane-bound, primary lysosomes. Large, dense, acid-phosphatase-positive residual bodies are formed which contain distorted remnants of mitochondria, endoplasmic reticulum and ribosomes. It is alleged that the primary release of lysosomal enzymes into the cytoplasm of viral-injured cells is responsible for cell death. This mechanism has been extensively studied in poliovirus infection in cell culture where it is suggested that a viral-induced protein damages lysosomal membranes allowing release of hydrolytic enzymes. Although lysosomal enzymes increase in the cell in relation to cytopathology and virion replication, this does not prove a causal relationship. Instead, it should be viewed as an autophagic response to the degeneration of other cell components.

Depletion of glycogen and other sources of energy is implicated in contributing to cell death, but how this affects critical enzyme systems is not known. Similarly, the description of 'cytotoxins' in viral infection is often discussed but the nebulous character of the data involved has prevented their contributing seriously to understanding how cells die during viral infection.

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DNA Viruses

Poxviruses

The complex DNA-containing poxviruses (table I) have an affinity for epidermis. Lesions begin as small intraepidermal foci of basal cell proliferation and end as circumscribed healing ulcers. Infected keratinocytes develop masses of virions that appear histologically as irregular acidophilic inclusion bodies. Inclusions stain poorly with the Feulgen technique for DNA, because of masking by other proteins.

Table I. Poxviruses

Vaccinia subgroup	*Avian pox subgroup*
Vaccinia	Fowlpox
Cowpox	Canarypox
Variola	Pigeonpox
Rabbitpox	Juncopox
Ectromelia	Flickerpox
Pseudoswinepox	*et al.*
Horsepox	
Buffalopox	*Ungrouped poxviruses*
Monkeypox	Swinepox
	Sealpox
Paravaccinia subgroup	Benign epidermal monkeypox
Orf (contagious ecthyma)	Molluscum contagiosum
Pseudocowpox	Sheeppox
Bovine papular stomatitis	Goatpox
	Lumpy skin disease (cattle)
Tumor subgroup	Raccoonpox
Myxoma	Elephantpox
Rabbit fibroma	Marsupialpox
Squirrel fibroma	
Yabapox	
Hare fibroma	

Ultrathin sections of pox virions reveal the basic structure to consist of: (1) a *core* (nucleocapsid), a shell of inner and outer membranes containing viral DNA; (2) an *intermediate coat*, an outer membrane and inner shell which expands into two lateral bodies, and (3) the *envelope* [DALES, 1963; DONATI *et al.*, 1965; MORGAN *et al.*, 1962]. A dense body is present adjacent to the inner shell. By negative staining, vaccinia virus, which is the prototype of the group, appears as a smooth-surfaced, brick-shaped particle of $300 \times 220 \times 100$ nm [NAGINGTON and HORNE, 1962; MÜLLER and PETERS, 1963].

The poxviruses have a common nucleoprotein antigen and are arranged into subgroups according to antigenic and other relationships, e.g., the vaccinia subgroup members are closely related serologically. The reactivation phenomenon – the ability of an intact, infectious poxvirus to reactivate a non-infectious (inactivated) virus – appears to be a general property of poxviruses [FENNER and WOODROOFE, 1960]. The protein coat of the viable virus is utilized to reactivate the second virus whose protein coat has been denatured through heat or ether treatment.

Vaccinia Subgroup

Cowpox

Cowpox is a self-limiting, mild disease of cattle characterized by vesiculopustular lesions of the udder and teats and slight serous lymphadenitis of the supramammary lymph nodes. Common in previous centuries in Western Europe, it was passed from cow to cow by infection of the milkman in whom it caused solid immunity against the far graver disease, smallpox. Cowpox is rarely seen today [GIBBS *et al.*, 1973] and in North America it has never been clearly documented.

Cowpox virus, when scarified onto the bovine teat, enters the epidermis and dermal mesenchyme. Following a latent period of 3–6 days, during which the scarifications heal, the cowpox lesion begins as a small, focal, non-elevated area of erythema, the *macule*. Proliferation of keratinocytes and subepidermal edema produces the *papule* which is an elevation of the lesion above the level of normal skin. Infected epidermal keratinocytes progressively enlarge, develop cytoplasmic inclusions and hydropic degeneration, and undergo lysis. Serous fluid accumulates in tiny cystic spaces or *vesicles* and these expand and coalesce. They soon become filled with neutrophils and fibrin and appear as the *pustule*. Pustules may erode to circumscribed ulcers

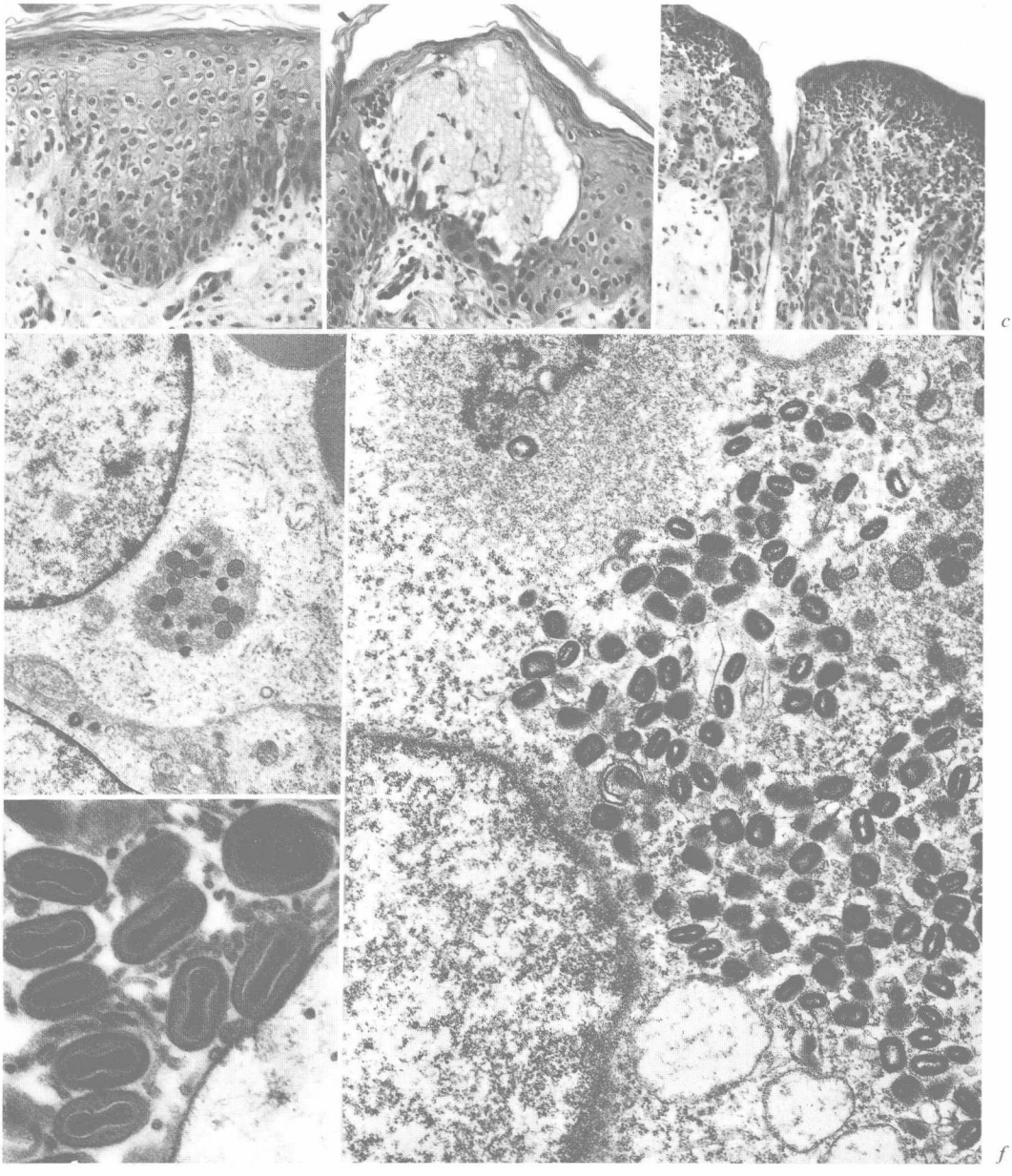

Fig. 1. Poxvirus: vaccinia subgroup. Progressive stages of cowpox lesions at top. *a* Papule (note tiny cytoplasmic inclusions). *b* Vesicle. *c* Pustule. *d* Viroplasmic factory with immature virions (B-type inclusion) in endothelial cell of subepithelial capillary. *e* Pox virions, ×46,875. *f* Epithelial cell with large inclusion body (type A) composed of mature virions, B-type inclusion (upper left), and pale nucleus (lower left), ×15,000.

but, barring complications, these lesions heal leaving a small hyaline connective tissue scar.

Cytopathology. The eosinophilic cytoplasmic inclusion bodies in infected cells (fig. 1) are small in comparison to the granular inclusions of the other poxviral subgroups. Ultrastructurally, they are found to be foci of dense granules ('A-type inclusions' or 'Downie bodies') which contain virions and intermediate viral particles. The granular material consists of entrapped monomeric ribosomes which are remnants of actively synthesizing polysomes present at the periphery of the inclusion [ICHIHASHI and DALES, 1973]. Smaller, irregular bodies of dense granular material ('viroplasmic factories' or 'B-type inclusions') which cannot be detected by light microscopy are also distributed throughout the cytoplasm. These are foci of early, viral-induced proteins surrounded by developing crescents of membranes which sequester viroplasm to form the initial viral particle.

Nuclear changes in infected cells include the margination of chromatin, disappearance of nucleoli and nuclear bodies, and pyknosis. Lysis of chromatin in the central area may leave a delicate web of filaments. In pustular lesions, masses of necrotic debris, fibrin and neutrophils obscure the viral-induced cellular changes.

Cowpox virus grows in cultured chick fibroblasts and HeLa cells. Differences in the containment of virions in the large inclusions allegedly varies in different cowpoxvirus strains and are used as discriminating genetic markers [ICHIHASHI and DALES, 1973]. Infected avian chorioallantoic membranes show extensive proliferation of ectoderm and mesoderm with development of large, compact cytoplasmic inclusion bodies [DOWNIE, 1939]. Cowpox is highly infective for rabbits and mice and large intravenous inocula produce generalized infection with skin rash, visceral lesions and lymphadenopathy [MIMS, 1968]. Lesions are initiated by replication of virus in endothelium. Viral antigens, as determined by immunofluorescent examination, are prominent in liver, ovary and other viscera in addition to the skin. Lymphoid tissues are depleted of lymphocytes, allegedly a phenomenon secondary to adrenal corticoid secretion [WALLNEROVA and MIMS, 1970].

Vaccinia

Vaccinia virus is scarified onto primate skin to prevent monkey pox and onto human skin to produce immunity to smallpox. The strains used for vaccination are stable laboratory viruses which have evolved from field isolates of cowpox virus by passage for generations on calf skin. Effective

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