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Demyelination in Allergic and Marek's Disease Virus Induced Neuritis Comparative Electron Microscopic Studies*

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Summary. Patterns of demyelination were studied in sciatic nerves, spinal roots and ganglia of chickens afflicted with either Marek's disease (MD) or experimental allergic neuritis (EAN). MD was induced in susceptible chicks after hatching by inoculation of the JM strain of MD Herpes virus. Tissues from these chickens were examined 7–83 days after infection. EAN was studied 10–21 days after sensitization of 4 week old chickens to emulsions containing human peripheral nerve with complete Freund's adjuvant. In both conditions lesions were encountered which consisted of perivenular infiltrates of mononuclear cells that penetrated the basal lamina of the neurolemmal sheath, displaced Schwann cells, lysed and stripped myelin lamellae without damage to axons. Other lesions in MD were characterized by lymphomatous infiltrates that contained necrotic cells and disintegrating axons. The similarity of the demyelinating process in MD to that seen in EAN suggests that MD virus infection activates lymphocytes sensitized to peripheral nerve myelin. The findings are discussed with reference to acute idiopathic polyneuritis (Guillain-Barré syndrome) in patients with preceding or concurrent Herpes virus infections including those known to cause lymphoproliferative disorders.

Key words: Marek's disease – Demyelination – Herpes virus – Allergic neuritis – Guillain-Barré syndrome.

Introduction

Marek's disease (MD) is a lymphoproliferative disorder of chickens caused by a Herpes virus (Biggs, 1973; Payne et al., 1976). Many organs are affected but the involvement of nervous tissue, particularly peripheral nerves is conspicuous (Marek, 1907). The neoplastic nature of the disease is apparent in some lesions but masked in others that are characterized by perivenular, mononuclear cell infiltrates and demyelination, i.e. changes similar to those seen in experimental allergic neuritis (EAN) (Siller, 1960; Petek and Quaglio, 1967, Prineas and Wright, 1972). These observations suggested that the unusual predeliction of the lymphomatous infiltrates for nervous tissue in MD might be determined by a preceding allergic inflammation of nerves triggered by MD virus induced autosensitization to peripheral nerve myelin. In the following report we compare lesions of peripheral nerves in MD with changes seen in EAN of chickens and confirm that the ultrastructural patterns of demyelination in MD are indistinguishable from those seen in EAN.

Materials and Methods

Marek's disease was studied in 80 chickens, RPRL line 7 obtained from the US Regional Poultry Research Laboratory, East Lansing, Michigan. The chickens were sacrificed 7–83 days after exposure to Marek's disease virus (MDV). The first group of newly hatched chicks were inoculated by the intraabdominal route with 10^3 PFU of cell associated preparation of RPRL clone 19 at the 20th serial passage in duck fibroblasts of the JM strain of MDV (Purchase et al., 1971; Courtesy of Dr. B. R. Burmester, Director, Regional Poultry Research Laboratory, East Lansing, Michigan). Further transmission to newly hatched chicks was accomplished by exposure to chickens afflicted with MD and by inoculation of fresh blood from affected chickens and cell suspensions from lymphomatous infiltrates of organs other than nerves. Chickens with MD were kept in housing separate from that of 20 normal control chickens and of those prepared for studies on EAN which was induced in 20 chickens at 4 weeks of age by intradermal injection of 0.2 ml of a homogenate containing 10% human peripheral nerve, complete Freund's adjuvant and pertussis vaccine. These chickens were sacrificed from 10–21 days after sensitization.

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The sciatic nerves, spinal root and ganglia were fixed by immersion in 2.5% phosphate buffered glutaraldehyde. Blocks from these specimens were post fixed in 1% buffered osmium tetroxide, dehydrated and embedded in Araldite. The remaining tissue was embedded in paraffin for light microscopic studies of sections stained with Hematoxylin Eosin, Luxol Fast Blue and Bodian's silver stain for axons. The Araldite embedded tissue was cut with Porter Blum and LKB microtomes. Thin sections were stained with uranyl acetate and lead citrate and examined with a Siemens 101 electron microscope operating at 80 kv.

Results

Allergic Neuritis

None of the 20 chickens sensitized to peripheral nerve myelin developed clinical signs of disease but lesions were detected in peripheral nerves, particularly in spinal roots and ganglia beginning at 15 days after sensitization. At 21 days 70% of the chickens had lesions in the peripheral nervous system but no changes in the brain, spinal cord or other organs. The lesions consisted of perivenular infiltrates of mononuclear cells that penetrated between endothelial cells, traversed the basement membrane and accumulated in the widened endoneurial space between myelinated axons. The cells consisted of small lymphocytes with scanty cytoplasm rich in ribosomes as well as larger cells with more abundant clear cytoplasm suggestive of lymphoblasts or macrophages (Fig. 1). Schwann cells within the cellular infiltrate often contained an increased number of ribosomes and mitochondria suggestive of a reactive or proliferative change. Some myelin sheaths around axons within or beyond the cellular infiltrate showed very uniform separations of myelin lamellae in the absence of degenerative alterations of Schwann cells (Fig. 6). The uniform lamellar separation that resulted in a doubling of the width between major dense lines, was caused by a split of the intraperiod line. Mononuclear cells were observed to pass through the basal lamina of the neurolemmal sheath and to penetrate into the outer mesaxon separating the Schwann cell from the myelin sheath. Disintegration or lysis of myelin lamellae affecting both compact and loose myelin sheaths occurred in contact with mononuclear cells (Fig. 7). The cytoplasm of the invading cells in direct contact with myelin lamellae was often devoid of organelles but filled with uniformly dispersed, fine granules (Fig. 7). The remnants of damaged internodal myelin segments were removed by macrophages that stripped individual myelin lamellae or compact portions of myelin sheaths off axons (Figs. 8 and 9). Completely demyelinated axons were surrounded by macrophages filled with myelin debris which could be distinguished from displaced, reactive Schwann cells that were rich in mitochondria, filaments and endoplasmic reticulum.

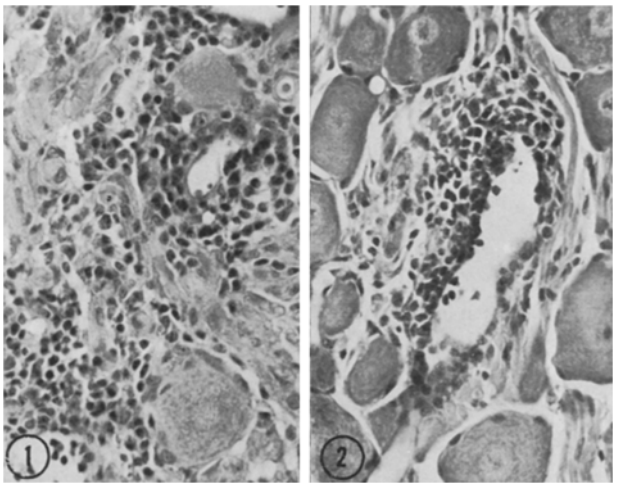

Fig. 1. Perivenular infiltrates of lymphocytes, lymphoblasts and macrophages in dorsal root ganglion of a chicken with EAN 21 days after sensitization to peripheral nerve antigen. H.-E. ×284

Fig. 2. Perivenular infiltrates of mononuclear cells in the dorsal root ganglion of a chicken 34 days after exposure to MD virus. H.-E. ×284

Neuritis in Marek's Disease

Chickens infected with Marek's disease virus (MDV) grew more slowly as compared to controls and often died suddenly. Clinical symptoms (drooping of wings, abnormal gait and paresis) developed in less than half of the affected birds usually in advanced stages, 5–6 weeks after exposure to MDV.

Histologic lesions were found in nerves as early as 16 days but more consistently beginning with 4 weeks after infection. The cellular infiltrates varied in appearance according to cell type and mode of spread. Three patterns were recognized. 1. There were perivenular infiltrates of mononuclear cells composed of lymphocytes, lymphoblasts and macrophages. Early lesions of this type frequently involved spinal roots and ganglia (Fig. 2). Paranodal and segmented demyelination was detected within the cellular infiltrates (Fig. 3). 2. There were less cellular, diffuse infiltrates of mononuclear cells including plasma cells which in places occupied the entire width of the nerve. These lesions occurred more frequently in advanced stages of the disease and were associated with widespread demyelination and Schwann cell proliferation (Fig. 4). 3. There were large compact aggregates of mononuclear cells including lymphoblasts and primitive reticulum cells with large nuclei. Necrotic cells were frequent within these infiltrates that showed a tendency

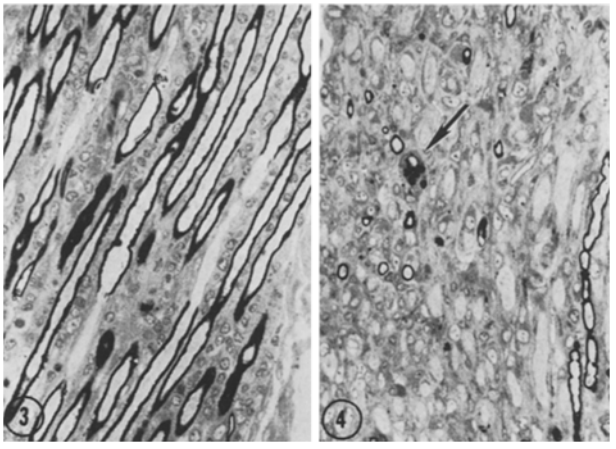

Fig. 3. Paranodal and segmental demyelination within a perivascular infiltrate of mononuclear cells in the spinal nerve root of a chicken 35 days after exposure to MD virus. Paraphenylene diamine × 518

Fig. 4. Widespread demyelination in the dorsal spinal root of a chicken 63 days after exposure to MD virus. Except for a few axons surrounded by intact sheaths and a single one showing ongoing demyelination (arrow) all others are completely demyelinated but surrounded by proliferated Schwann cells. Paraphenylene diamine × 389

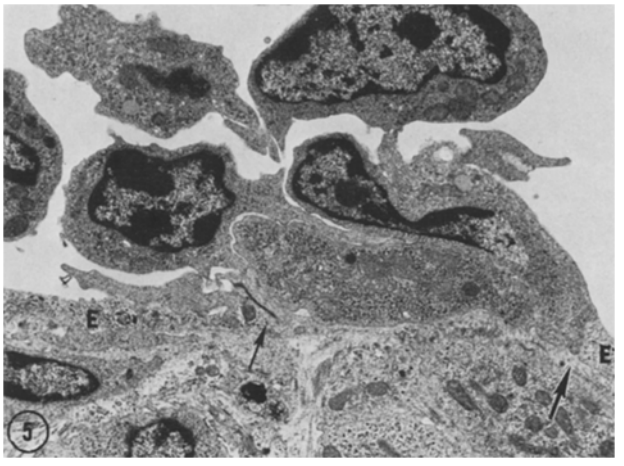

Fig. 5. Attachment of small lymphocytes to the endothelium (*E*) of a venule in the dorsal root ganglion of a chicken 33 days after exposure to MD virus. The lymphocytes traversed the vessel wall by passing through focal gaps between endothelial cells (big arrow) which in other places remained tightly joined (small arrow). × 8100

to displace and compress the surrounding nerve fibers. Axonal degeneration associated with secondary myelin disintegration occurred within and distal to these lymphomatous nodules. Lesions of this latter 'neoplastic' type could be detected within the same nerve next to 'inflammatory' infiltrates. Similar compact nodules of mononuclear cells were found in the spinal cord and brain as well as in other organs particularly the gonads, lungs, liver, kidneys, heart and lymphoid tissue. No lesions were encountered in control chickens.

Electron microscopic studies included an extensive search for virus particles and early parenchymal changes prior to the infiltration of mononuclear cells, i.e. in chickens sacrificed up to 2 weeks after infection. No virus was detected and there were no changes of Schwann cells, myelin sheaths or axons except for artefactitious alterations in some inadequately preserved specimens consisting of ruffled myelin sheaths and hydropic Schwann cells with dilated, disrupted endoplasmic reticulum and vacuolated mitochondria.

Ongoing primary demyelination was detected within perivenular mononuclear cell infiltrates in early and advanced stages of Marek's disease. The invading cells were derived from small circulating lymphocytes with scanty, ribosome rich cytoplasm. The cells attached to the vessel wall (Fig. 5), penetrated between endothelial cells and through the vascular basement membrane. Within the endoneurium the invading

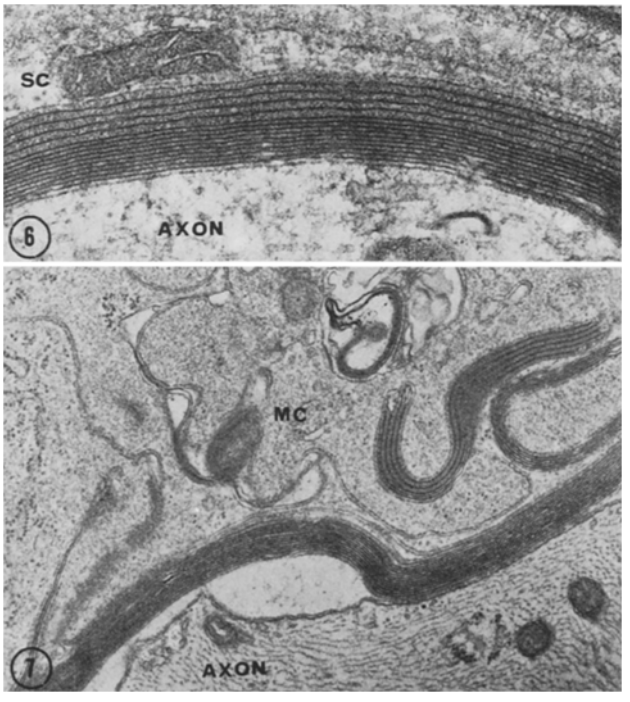

Fig. 6. Uniform separation of the outer myelin lamellae of a myelin sheath surrounded by a normal Schwann cell (*SC*) in the dorsal root ganglion in EAN 21 days after sensitization to peripheral nerve myelin. × 40165

Fig. 7. Lysis of the outer myelin lamellae in contact with cytoplasmic processes of a mononuclear cell (*MC*). Fragments of myelin sheath show uniform separation of some of their lamellae. Also note the lack of organelles but the presence of abundant dust-like granules in the cytoplasmic tongues of the invading mononuclear cell. × 20083

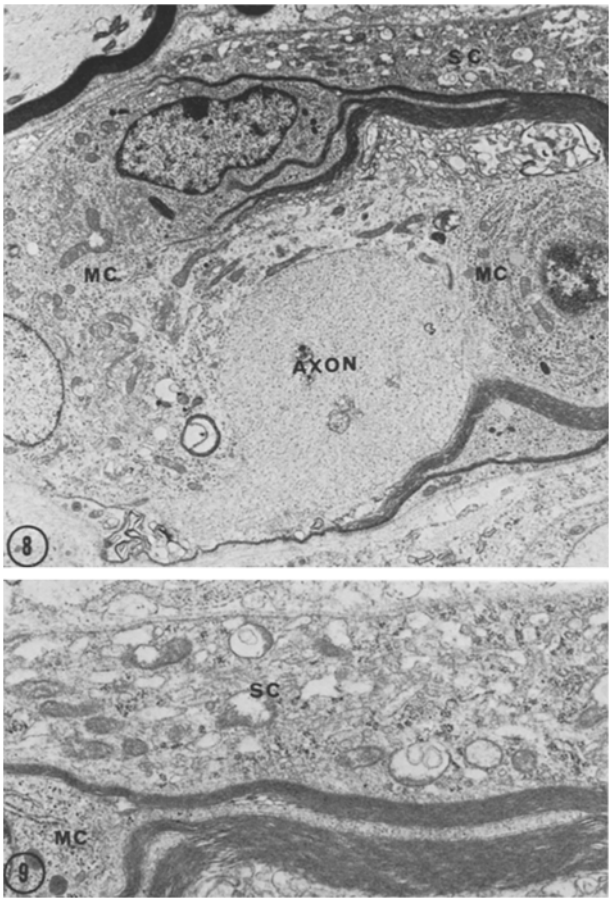

Fig. 8. Stripping of a damaged myelin sheath by mononuclear cells (*MC*) with abundant cytoplasm containing phagosomes suggestive of macrophages. The Schwann cell (*SC*) remained intact but shows reactive changes that are enlarged in Figure 9. EAN 21 days after sensitization. × 6750

Fig. 9. Higher magnification of the invading tongue of a mononuclear cell (*MC*) that is penetrating into a damaged myelin sheath. The covering Schwann cell (*SC*) shows reactive changes consisting of an increase in ribosomes, endoplasmic reticulum and mitochondria that show artefactitious vacuolation. × 20250

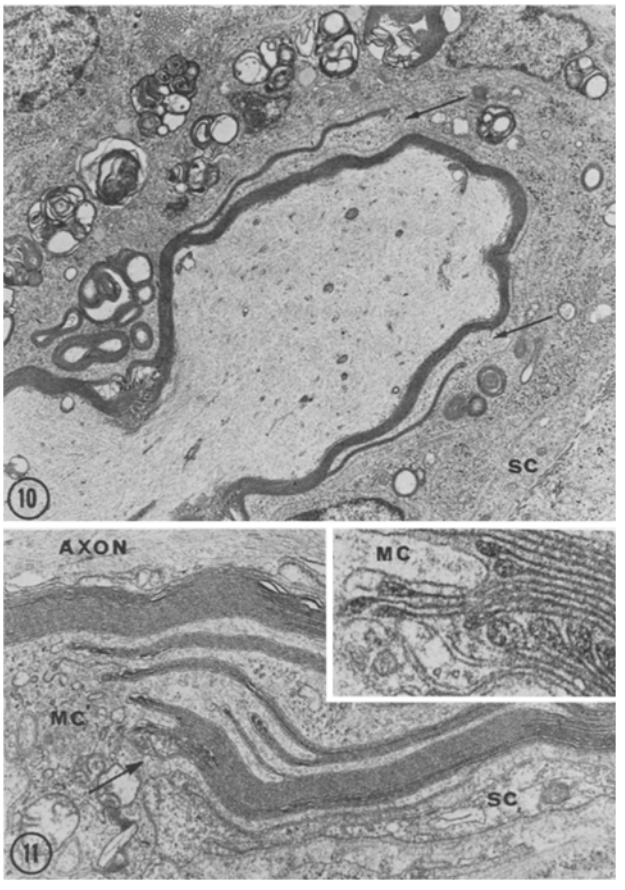

Fig. 10. Stripping of a myelin sheath by macrophages that penetrate the sheath (arrows) after lysis of the outermost lamellae. The Schwann cell (*SC*) is displaced by the invading cells. Thirty-five days after exposure to MD virus. × 5445

Fig. 11. Stripping of uniformly separated myelin lamellae at a node of Ranvier by cytoplasmic processes of an invading mononuclear cell (*MC*). The Schwann cell (*SC*) remained intact. × 13613. Arrow points to area that is enlarged in inset showing intact cytoplasmic loops of terminating myelin lamellae. Thirty-five days after exposure to MD. × 40840

cells displayed more abundant cytoplasm with less condensed ribosomes. Similar to observations in allergic neuritis, some Schwann cells within the cellular infiltrate showed reactive changes characterized by an increased number of mitochondria, ribosomes and endoplasmic reticulum. The uniform separation of myelin lamellae was also observed but only in sheaths that were already invaded by mononuclear cells that penetrated through the basal lamina into the outer mesaxon displacing the Schwann cell from its sheath. Invasion of sheaths also occurred at nodes of Ranvier. Myelin sheaths were lysed when in contact with the invading cells. Stripping of individual myelin lamellae or compact portions of the sheath by invading cells was noted (Figs. 10 and 11). Completely demyelinated axons surrounded by macrophages filled with myelin debris (Fig. 12) were common within the cellular infiltrates.

Nerves diffusely infiltrated by mononuclear cells often revealed large fields of demyelinated axons (Fig. 4). Ongoing demyelination was rarely seen in these nerves. The demyelinated axons were surrounded by proliferated Schwann cells. Occasional axons were covered by thin myelin sheaths suggestive of remyelination. Abundant collagen fibers and scattered mononuclear cells including plasma cells were encountered within the endoneurium between the demyelinated axons.

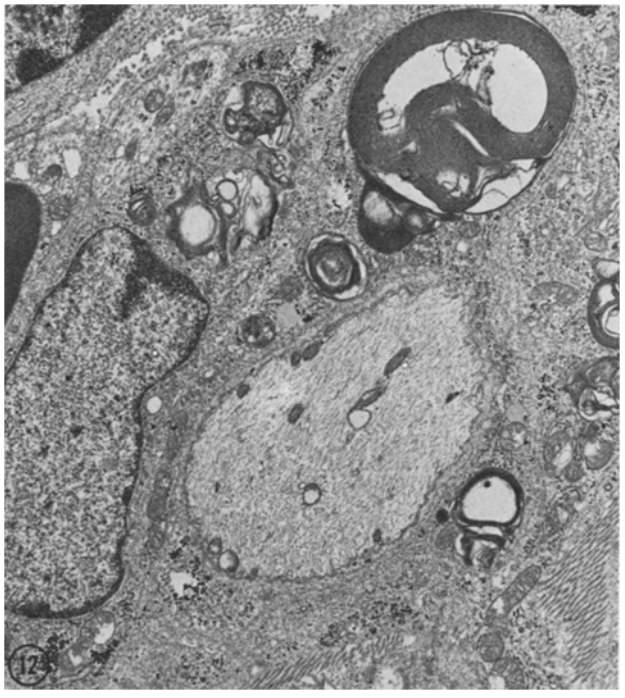

Fig. 12. Completely demyelinated axon surrounded by a macrophage containing myelin debris in sciatic nerve of a chicken 63 days after exposure to MD virus. ×13888

The lymphomatous lesions were composed of compact aggregates of cells containing numerous necrotic nuclei and cytoplasmic debris. Degenerated axons and collapsed, disrupted myelin sheaths surrounded by disintegrating Schwann cells were occasionally noted within these cellular infiltrates. Many of the 'neoplastic' cells showed bizarre nuclear configurations including long filiform projections. No virus particles were detected.

Discussion

Most light microscopic studies on MD emphasize the occurrence of two distinct types of peripheral nerve lesions, one inflammatory, the other neoplastic (Payne et al., 1976). In addition a third type consisting of diffuse scanty cellular infiltrates often involving the entire width of edematous nerves has been mentioned (Payne and Biggs, 1967; Wight, 1969; Fujimoto et al., 1971). Our studies confirmed these observations showing that demyelination with preservation of axons developed within the perivenular 'inflammatory' lesions whereas cell necrosis and axonal degeneration with secondary myelin breakdown occurred within the 'neoplastic' infiltrates. Nerves widely infiltrated by lymphocytes, plasma cells and macrophages contained abundant demyelinated axons including some surrounded by thin myelin sheaths indicative of remyelination. These findings were interpreted as a more advanced stage of the 'inflammatory' lesion in accordance with the view held by other investigators (Payne et al., 1976).

The pathogenesis of the inflammatory lesion in MD resembled that seen in EAN. In both conditions, early lesions frequently involved spinal roots and ganglia which most likely reflects the facilitated permeability of vessels in these regions as demonstrated in many species including fowl (Olsson, 1971). Small lymphocytes and macrophages traversed the wall of venules. Proliferation and transformation of cells to lymphoblasts occurred in the endoneurium. The cells penetrated through the neurolemmal basal lamina and displaced Schwann cells from myelin sheaths. The displacement of Schwann cells associated with reactive cytoplasmic changes might be responsible for the retraction of myelin lammellae at nodes of Ranvier accounting for paranodal demyelination as described in early lesions of EAN (Cragg and Thomas, 1964). When in contact with presumably sensitized mononuclear cells, myelin sheaths disintegrated whereas the displaced Schwann cells remained intact except for showing reactive cytoplasmic alterations consisting of an increased amount of ribosomes and endoplasmic reticulum. This selective destruction of myelin sheaths, the target of the allergic reaction, has been recognized as a characteristic finding in EAN (Lampert, 1969; Wisniewski et al., 1969; Schroeder and Krücke, 1970). In places, the lysis of myelin lamellae was preceded by a uniform separation of the lamellae (Fig. 6) as previously documented in allergic encephalomyelitis (Lampert, 1967) and as described in myelinated organ cultures after exposure to sera containing antimyelin antibodies (Bornstein and Raine, 1976). The significance of this observation is obscure but it may indicate that myelin lamellae must first be primed by antibody before becoming susceptible to cell mediated lysis. Remnants of damaged sheaths were removed by macrophages that stripped myelin lamellae off axons. The same pattern of demyelination has previously been observed in nerves of 8 weeks old field chickens afflicted with spontaneous MD (Prineas and Wright, 1972) and is here confirmed in experimentally induced MD and EAN.

Further evidence of a cell mediated immune response to myelin in MD has come from studies showing that affected chickens develop a delayed type of hypersensitivity reaction to myelin as demonstrated by skin tests (Schmahl et al., 1975). In addition, the transfer of splenic cells from chickens with MD induced nerve lesions in normal chickens within 6 days whereas a similar inoculation of MD virus

preparations required more than 14 days to cause a neuropathy (Hoffmann-Fezer et al., 1975). In this regard it is also of interest to note that thymus derived T-cells predominate in the cellular infiltrates (Rouse et al., 1973) and that thymectomy decreased the proportion of chickens with lymphoproliferative nerve lesions (Payne et al., 1976) whereas removal of the B-cell harboring bursa of Fabricius had either no effect (Payne and Rennie, 1970) or enhanced disease (Carte et al., 1969; Morris et al., 1969).

Theories concerned with possible mechanisms that could induce sensitization of lymphocytes to peripheral nerve myelin in MD include: 1. release of myelin antigens after damage to Schwann cells or myelin sheaths prior to the development of the inflammatory lesion, 2. incorporation of myelin antigens in the viral envelope which implies maturation of virus in myelin forming cells, 3. interference with the suppression of pre-existing sensitized cells resulting in the activation of latent hypersensitivity.

Our studies provided no evidence for the first two hypotheses. Other investigators have described changes in Schwann cells and myelin sheaths which preceded cellular infiltrates and suggested that demyelination might occur secondary to Schwann cell damage (Wight, 1969; Payne et al., 1976). We failed to detect changes of nerve fibers prior to the invasion of mononuclear cells. We were also unable to find virus particles within nerves. Virus is prominent in lymphoid tissue early after infection and persists in leukocytes but is rarely detected in nerves (Aldlinger and Calnek, 1973). Virus particles have been illustrated in cells that were interpreted as Schwann cells (Calnek et al., 1970; Ubertini and Calnek, 1970) but the depicted cells lack a covering basement lamina and do not enclose axons suggesting that they represent infiltrating lymphoid cells rather than Schwann cells. Persistence of Herpes virus in peripheral nervous tissue is, however, well documented in other species (Stevens and Cook, 1971; Stevens et al., 1972) including man (Baringer and Swoveland, 1973), and our failure to find recognizable viral particles in Schwann cells does not rule out latent infection.

The speculation that MD virus infection may subdue humoral or cellular mechanisms that normally suppress cells sensitized to the host's own antigens is based on the observation that chickens afflicted with MD reveal evidence of depressed immune responses (Purchase et al., 1968; Burg et al., 1971; Calnek et al., 1975) which increase their susceptibility to other diseases (Biggs et al., 1968). Further, lymphoid cells from chickens with MD demonstrate a reduced response to mitogenic stimuli (Lu and Lapen, 1974). This apparent paradox of observing cell mediated hypersensitivity to myelin in the presence of a demonstrated impairment of cellular immune mechanisms can be reconciled if one accepts the concept of a selective depression of lymphoid cells. It is well known that viruses grow in lymphoid cells and that they interfere with cellular and humoral immune responses including the suppression of specific immunoglobulins (Notkins et al., 1970). In EAN protective antibodies develop that suppress the activity of lymphoid cells sensitized to myelin (Lehrich and Arnason, 1971). The removal of the antibody producing bursa of Fabricius in chickens with MD resulted in enhancement of the disease (Carte et al., 1969; Morris et al., 1969). Virus infection as well as infiltration of the bursa by neoplastic lymphoid cells occur in MD and could selectively affect humoral mechanisms that might be involved in blocking the activity of sensitized cells. A disturbance in the regulation of interactions between immunocompetent cells may also play a role in the pathogenesis. Subpopulations of T-cells including helper and suppressor cells have been recognized (Dutton, 1976). By selectively depressing suppressor cells it has been possible to enhance the immune response in mice to implanted tumors (Cohen and Feldmann, 1975). Demyelination in EAN is usually confined to perivascular regions and animals recover indicating that the demyelinating process is arrested soon after onset. In contrast in MD very diffuse, widespread demyelination involving the entire width of a nerve are encountered which could reflect an impairment of humoral or cellular mechanisms that control the activity of sensitized cells.

A comparison of our findings in MD to those seen in man in acute idiopathic polyneuritis or the Landry Guillain Barré Strohl syndrome (GBS) is of interest because this condition also; 1. shows ultrastructural patterns of demyelination indistinguishable from that seen in EAN, 2. occurs following Herpes virus infections, 3. accompanies lymphoproliferative disorders, and 4. develops in immunosuppressed patients.

A cell mediated immunity directed against peripheral nerve myelin can be demonstrated in GBS (Currie and Knowles, 1971; Behan et al., 1972). Acute lesions are characterized by perivenular infiltrates of mononuclear cells and demyelination (Ashbury et al., 1969). Electron microscopic studies revealed lysis and stripping of myelin lamellae in contact with lymphoblasts and macrophages. Further, similar to the findings in EAN and MD the Schwann cells were displaced by the invading cells that selectively destroyed myelin sheaths (Wisniewski et al., 1969; Carpenter, 1972; Prineas 1972). This pattern of demyelination can be distinguished from that seen in neuropathies caused by a primary damage to Schwann cells, e.g. after intoxications with lead (Lampert and

Schochet, 1968), tellurium (Lampert and Garrett, 1971) or diphtheria toxin (Weller, 1965).

Antecedent events related to the onset of GBS range from viral, mycoplasmal and bacterial infections to surgery, vaccination, fever treatment and other stressful conditions (Arnason, 1975). Since MD is caused by a Herpes virus it is significant to note that GBS has been described following infections with Herpes zostervaricella virus (Knox et al., 1961; Welch, 1962; Dayan et al., 1972; Zivin and Schwager, 1972), cytomegalovirus (Klemola et al., 1967), Herpes simplex (Olivarius and Buhl, 1975) and more frequently with Epstein Barr virus (Dowling and Cook, 1974; Grose et al., 1975). The association of GBS with infectious mononucleosis had been recognized (Rikker et al., 1947; Melnick and Flewett, 1964; Gautier-Smith, 1965) long before Epstein Barr virus was implicated as the etiologic agent of glandular fever (Henle et al., 1968). GBS has also been observed in neoplastic lymphoproliferative disorders (Borit and Altrocchi, 1971) notably Hodgkin's disease (Cameron et al., 1958; Klingon, 1965; Lisak et al., 1977) which is of particular interest because of the similarity to MD. As in MD immunologic responsiveness is depressed in these patients (Lisak et al., 1977), yet hypersensitivity to peripheral nerve antigen develops. GBS has also been reported in a renal transplant recipient who received immunosuppressive therapy (Drachman et al., 1970). The selective suppression of humoral or cellular immune mechanisms that control latent hypersensitivity may well be the common denominator responsible for the development of GBS following such diverse, stressful events as viral infections, vaccinations, surgery and pregnancy (Arnason, 1975; Lisak et al., 1977).

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