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# Pathology of the Choroid Plexus in Spontaneous Immune Complex Disease and Chronic Viral Infections*

Peter W. Lampert and Michael B. A. Oldstone

Department of Pathology, University of California, San Diego and
Department of Experimental Pathology, Scripps Clinic and
Research Foundation, La Jolla, California

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*Summary.* Using immunofluorescence and electron microscopy, deposits of immunoglobulin G (IgG) and the third complement component (C3) are found in the choroid plexus of mice with spontaneous immune complex disease, in mice chronically infected with lymphocytic choriomeningitis (LCM) virus and in patients with systemic lupus erythematosus (SLE). (NZB × W) $F_1$ mice develop antibodies to nuclear antigen (ANA) and DNA (ADNA) and are an animal model of human SLE. Enhancement of ANA and ADNA responses by immunization with DNA leads to accelerated and more severe involvement of the choroid plexus accompanied by leukocytic infiltrates. Mice infected *in utero* or at birth with LCM virus harbor the virus throughout life and continuously produce antibodies. Virus and antiviral antibody(s) combine in the serum and form immune complexes that are trapped in renal glomeruli and choroid plexus. In contrast, mice chronically infected with scrapie fail to show immunoglobulin deposits in choroid plexus and brain despite clinical and pathological evidence of severe scrapie encephalopathy. The findings indicate that the choroid plexus is a favored site for the trapping of immune complexes and may be damaged during immune complex disease. Choroid plexus injury could lead to spinal fluid changes that may be responsible in part for neurologic and psychiatric disturbances seen in patients with systemic lupus erythematosus, chronic and acute viral infections and other disorders associated with circulating antigen-antibody complexes.

## Introduction

Entrapment of circulating antigen-antibody complexes in renal glomeruli and the subsequent development of glomerulonephritis are well documented in a variety of immune complex diseases, notably systemic lupus erythematosus (SLE) and experimental serum sickness (reviewed by Cochrane and Koffler, 1973). Deposits of immune complexes also play a major role in the pathogenesis of tissue injury in chronic viral infections (reviewed by Oldstone, 1974). Nephritis and arteritis due to deposits of virus or virus induced antigen-antiviral antibody complexes have been described in human infections with hepatitis B virus (Australian Antigen disease) (Nowoslawski *et al.*, 1972), measles virus (subacute sclerosing panencephalitis) (Dayan and Stokes, 1972), Epstein-Barr virus (Infectious mononucleosis and Burkitt's lymphoma) (Makojima *et al.*, 1974), in murine infections with lymphocytic choriomeningitis virus (Oldstone and Dixon,

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1967, 1969), lactic dehydrogenase virus (Porter and Porter, 1971; Oldstone *et al.*, 1972), polyoma virus (Tonietti *et al.*, 1970), coxsackie B virus (Sun *et al.*, 1967), in mink infections with Aleutian disease virus (Porter *et al.*, 1969) and in horse infections with equine infectious anemia virus (Banks *et al.*, 1972). Since the choroid plexus has a filtering function akin to that of the renal glomerulus, immune complexes might also be trapped in the plexus. This has been demonstrated in several patients with SLE (Atkins *et al.*, 1972; Lampert and Oldstone, 1973) and in experimental serum sickness (Koss *et al.*, 1973). Injury to the choroid plexus may interfere with normal spinal fluid formation which in turn can lead to mental disturbances (Collip, 1920; Huggins and Hastings, 1932), a prominent clinical finding in patients with SLE (Johnson and Richardson, 1968). Our studies were designed to determine whether deposits of immunoglobulins occur in the choroid plexus in: 1. Spontaneous autoimmune disease of (NZB × W) $F_1$ mice in which circulating complexes of specific antibodies combined with nuclear antigen (ANA) and DNA (ADNA) form (Lambert and Dixon, 1968); 2. Persistent murine infection with lymphocytic choriomeningitis virus (LCM) in which circulating virus-antiviral antibody complexes occur (Oldstone and Dixon, 1969); 3. Mouse scrapie in which as yet no evidence exists of specific immune complex formation or other host immune reactions (Lampert *et al.*, 1972). In addition, preliminary findings on human postmortem choroid plexus are reported.

## Materials and Methods

Female (NZB × W) $F_1$ mice were sacrificed at monthly intervals from 1 to 9 months of age. Another series of 4 to 6 week old female (NZB × W) $F_1$ mice were injected at 14 day intervals (3 ×) with 25 mg DNA methylated bovine serum albumin (DNA-m-BSA). Control mice were immunized with methylated bovine serum albumin. Plasma antibodies to DNA (ADNA) were determined by a modified Farr antigen binding assay (Dixon *et al.*, 1971) and antibodies to nuclear antigens (ANA) were tested on normal mouse kidney sections by the indirect immunofluorescent technic (Lambert and Dixon, 1968).

Mice of different strains (SWR/J, C3H.Q, NZB, NZW and HAICR) were inoculated intracerebrally within 18 hours after birth with LCM virus (100 × $LD_{50}$) (Oldstone and Dixon, 1969). Their kidneys and brains were examined at 4 months (30 mice) and up to 12 months of age (30 mice).

A total of 77 HAICR mice of both sexes were studied, 50 chronically infected with scrapie agent and 27 controls. The mice were infected at 4 weeks of age by intraperitoneal injection of 0.1 ml of a 20% lyophilized spleen suspension from scrapie mice (courtesy of Dr. C. J. Gibbs, Jr.). Beginning at 2 months of age, groups of infected and control mice were studied at monthly intervals until onset of disease 8 to 10 months after inoculation.

For immunofluorescence, half of the brains and kidneys of mice were frozen in liquid nitrogen. Frozen sections were stained with fluorescent labeled rabbit antibody to mouse immunoglobulin G (IgG), third complement component (C3), fibrinogen and albumin. In the study of (NZB × W) $F_1$ mice, immunoglobulins were eluted from frozen sections in citrate-HCl buffer or 2M potassium chloride (KCl). The eluted sections were incubated with fluoresceinated antibody to DNA. Adjacent sections were treated with DNase prior to exposure to ADNA. In addition mice chronically infected with LCM virus (carrier mice) were examined for the presence of LCM virus antigens with monospecific fluoresceinated guinea pig antibody to LCM virus. Methods of sectioning, staining, making various conjugates and elution technics have been reported (Lambert and Dixon, 1968; Oldstone and Dixon, 1969).

For electron microscopy the choroid plexus of mice was removed with the aid of a dissecting microscope from the lateral and 4th ventricle of the other half of the brain that had been immersed for one hour in 5% phosphate buffered glutaraldehyde. Except for a few controls, the choroid plexus was prepared for electron microscopy only when immunoglobulins were

seen by immunofluorescence. The plexus was post fixed in 1% phosphate buffered osmium tetroxide, dehydrated and embedded in Araldite. Sections were cut with a LKB microtome, stained with uranyl acetate and lead citrate and examined with a Siemens Elmiscop 101 operating at 80 kV.

Human choroid plexus were removed at autopsy from three patients with SLE who had neuropsychiatric disturbances. Another 20 postmortem choroid plexus were obtained within 12 hours of death from patients without evidence of immune complex disease or neurologic disorders. The tissue was prepared for immunofluorescence and electron microscopy according to the above mentioned procedures. Frozen sections were stained with fluoresceinated rabbit antibody to human IgG and C3.

## Results

*Female (NZB × W) $F_1$ Mice.* Granular deposits of IgG, C3 but rarely fibrinogen and not albumin were found in renal glomeruli throughout the mesangia and capillary loops in all mice after 3 months of age. By 6 months of age, mice having severe glomerulonephritis also had fibrinogen but not albumin deposits in the mesangia and along the glomerular basement membrane. No IgG deposits were revealed in the choroid plexus until the animals were 4 months old. At 5 and 8 to 9 months of age IgG was present in the choroid plexus in 50 and 80 percent of the mice, respectively (15 mice in each group). Unless studied by immunofluorescence, the choroid plexus of these mice appeared normal by light microscopy, in particular there were no leukocytic infiltrates. The IgG deposits occurred as irregular, granular, brightly fluorescent aggregates. C3 was less consistently detected and there was no staining of the deposits with fluoresceinated antibodies to albumin and fibrinogen. After antibody elution in citrate or KCl buffer and incubation of the sections with fluoresceinated antibody to DNA, staining of nuclei and perivascular stroma was obtained which was abolished by prior exposure of the sections to DNase. A continuous rise of the plasma antibody level of ANA and ADNA in these mice preceded the increased incidence of IgG deposits in the choroid plexus.

Repeated immunization of 4 to 6 week old (NZB × W) $F_1$ mice with DNA-m-BSA increased the ADNA titer at an earlier age resulting in deposits of IgG in renal glomeruli and choroid plexus of all mice at 3 to 4 months of age (Figs. 1–4). Leukocytic infiltrates consisting of mono- or polymorphonuclear cells were detected in the affected choroid plexus in some of these mice (Fig. 3). In contrast, litter mates immunized with methylated bovine serum albumin showed no choroid plexus lesions.

Electron microscopy of the renal glomeruli revealed large deposits of electron dense material beneath the endo- and epithelium as well as within the basement membrane (Fig. 2). The choroid plexus contained irregular electron dense clumps mainly within perivascular spaces (Fig. 5) but occasionally also within or adjacent to the endo- or epithelial basement membrane. Extracellular, electron dense deposits were rarely detected in choroid plexus with leukocytic infiltrates of mice immunized with DNA-m-BSA (Fig. 6).

*Mice Chronically Infected with LCM Virus.* All 4 to 12 month old mice of the various strains showed IgG and C3 in the renal glomeruli. By 4 months of age 40% (6 out of 15) had IgG deposits in the choroid plexus. At 9 to 12 months of age all 30 mice showed IgG as well as viral antigen and C3 in a patchy irregular

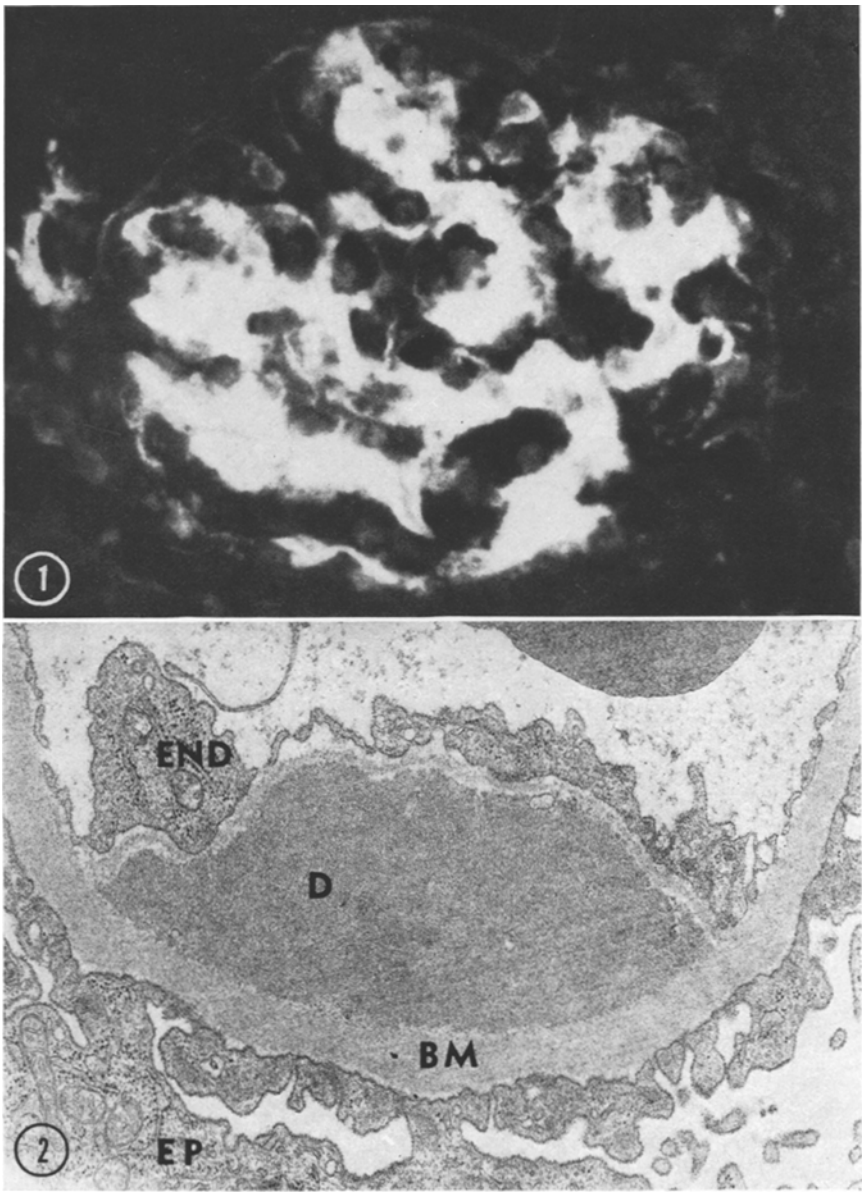


Fig. 1. IgG deposits in renal glomerulus of a 4 month old female (NZB × W) $F_1$ mouse that received repeated injections of DNA-m-BSA. Frozen sections stained with fluorescent rabbit antibody to mouse IgG. × 500

Fig. 2. Electron dense deposit (*D*) in the basement membrane (*BM*) of a glomerular loop from the same kidney as depicted in Fig. 1. × 2500

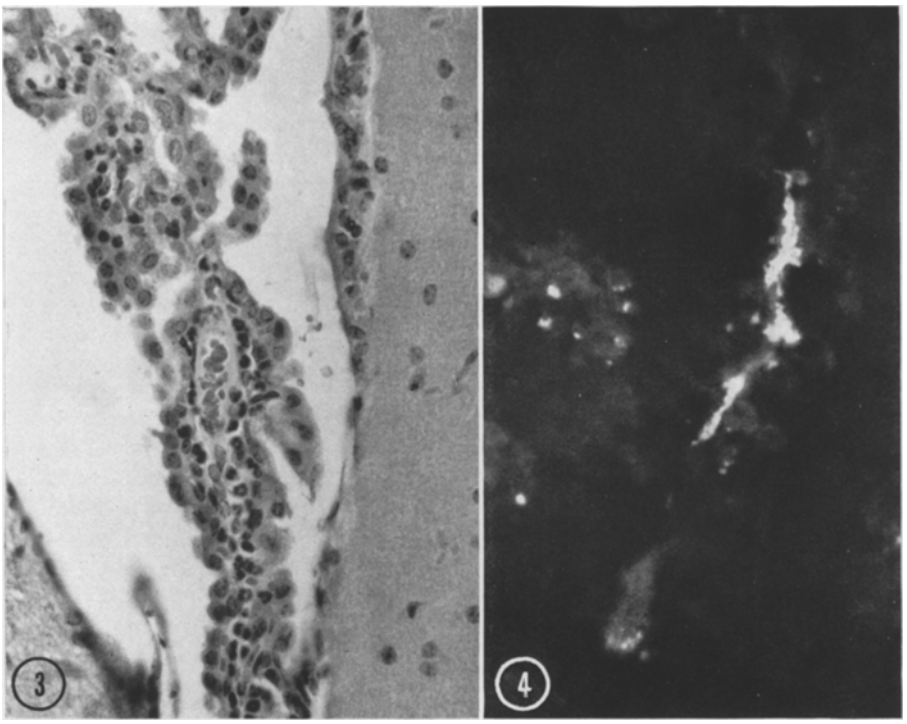


Fig. 3. Polymorphonuclear leukocytes in choroid plexus of a 4 month old female (NZB × W) $F_1$ mouse that received repeated injections of DNA-m-BSA. × 250

Fig. 4. IgG deposits in choroid plexus from the same mouse as depicted in Fig. 3. Frozen section stained with fluorescent rabbit antibody to mouse IgG. × 250

distribution in the plexus (Fig. 7). Fluoresceinated antibodies to albumin and fibrinogen did not stain the choroid deposits. Mononuclear cell infiltrates were occasionally observed.

Electron microscopy demonstrated electron dense masses predominantly in perivascular spaces (Fig. 8). Occasionally fragments of cell membranes and degenerated cytoplasm containing ribosomes were intermixed with the electron dense material. Phagocytosis of the deposits were noted in a choroid plexus that contained mononuclear cell infiltrates (Fig. 9).

Whereas it was possible to elute, recover and immunochemically identify specific LCM antibodies from complexes trapped in renal glomeruli (Oldstone and Dixon, 1969), this was not achieved with the choroid plexus owing to the scattered and small amounts of IgG in the rather small tissue sample of mouse choroid plexus.

*Mice Infected with Scrapie Agent.* Slight staining of renal glomeruli for the presence of IgG became apparent in a few mice at 2 months of age. By 5 months all control and scrapie infected mice revealed slight granular deposits of IgG in the glomerular loops and mesangium of renal glomeruli. In contrast, the

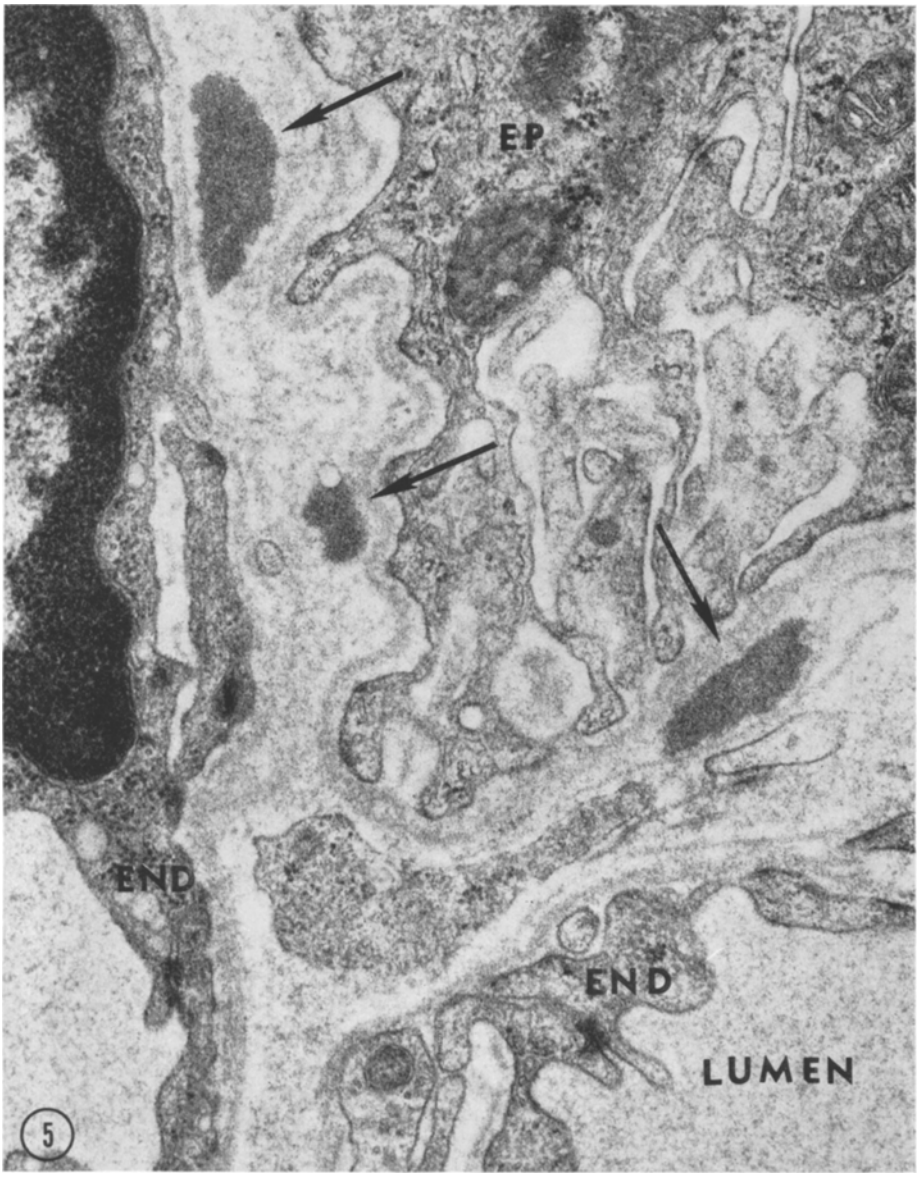


Fig. 5. Electron dense deposits (arrows) in the perivascular space of the choroid plexus of a 8 month old (NZB × W) $F_1$ female mouse. *END* endothelium, *EP* epithelium. × 25000

choroid plexus failed to show IgG deposits in 50 scrapie infected and 27 control mice. Notably, no deposits were revealed even in moribund scrapie mice at 8 to 10 months of age. At this stage, over 90% of the mice showed morphologic evidence of scrapie encephalopathy i.e. widespread status spongiosus and gliosis throughout the gray matter without leukocytic infiltrates (Lampert *et al.*, 1971).

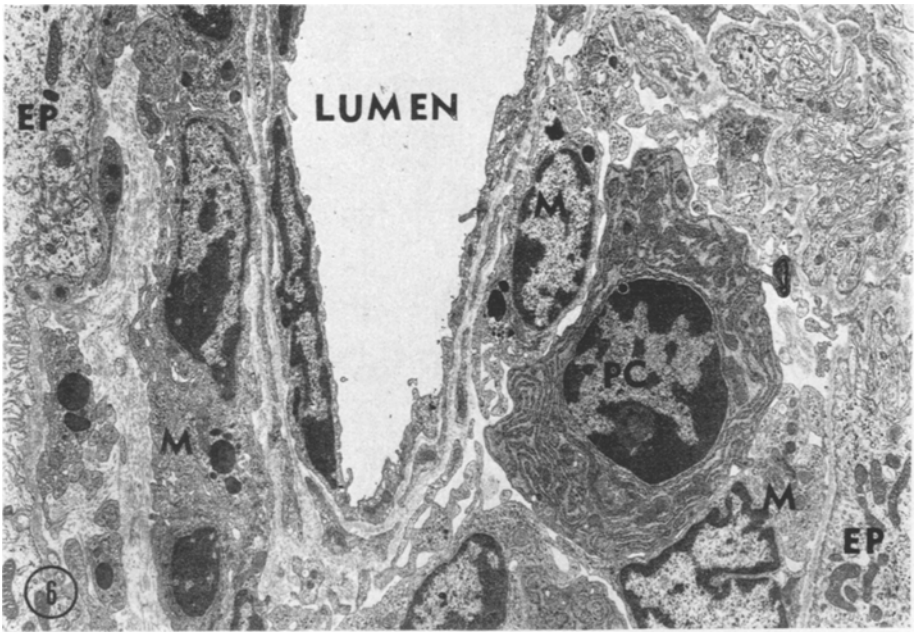


Fig. 6. Mononuclear cell infiltrates in the perivascular space of a 4 month old female (NZB $\times$ W) $F_1$ mouse that received repeated injections of DNA-m-BSA. Electron dense inclusions are seen in macrophages (*M*) but there are no deposits in extracellular spaces. *PC* plasma cell. $\times$ 8000

*Human Postmortem Choroid Plexus.* All three patients with systemic lupus erythematosus revealed patchy granular deposits of IgG and C3 in their choroid plexus (Fig. 10) and renal glomeruli. Leukocytic infiltrates were observed in the plexus of one of these patients. By electron microscopy, electron dense deposits were found in all 3 patients with SLE in perivascular spaces and attached to the epithelial basement membrane (Fig. 11). The choroid plexus from 20 patients without clinical evidence of immune complex disease or neurologic disorders ranging in age from 43 to 85 years of age showed IgG deposits in 5 cases but these failed to react with fluorescent anti-C3-antibody. Further studies are in progress to determine the incidence of immunoglobulin deposits in consecutive autopsies with particular reference to age, chronic viral infections and other autoimmune diseases.

## Discussion

The findings indicate that immunoglobulins are trapped within the choroid plexus in diseases that are known to be associated with circulating antigen-antibody complexes. In (NZB $\times$ W) $F_1$ mice the incidence of the deposits could be correlated with a rise of antibodies to ANA and DNA, particularly in mice that were immunized with DNA-m-BSA. The involvement of the choroid plexus occurred later and was less intense than the renal lesions. The granular pattern of the deposited complexes, presence of IgG, third complement component and

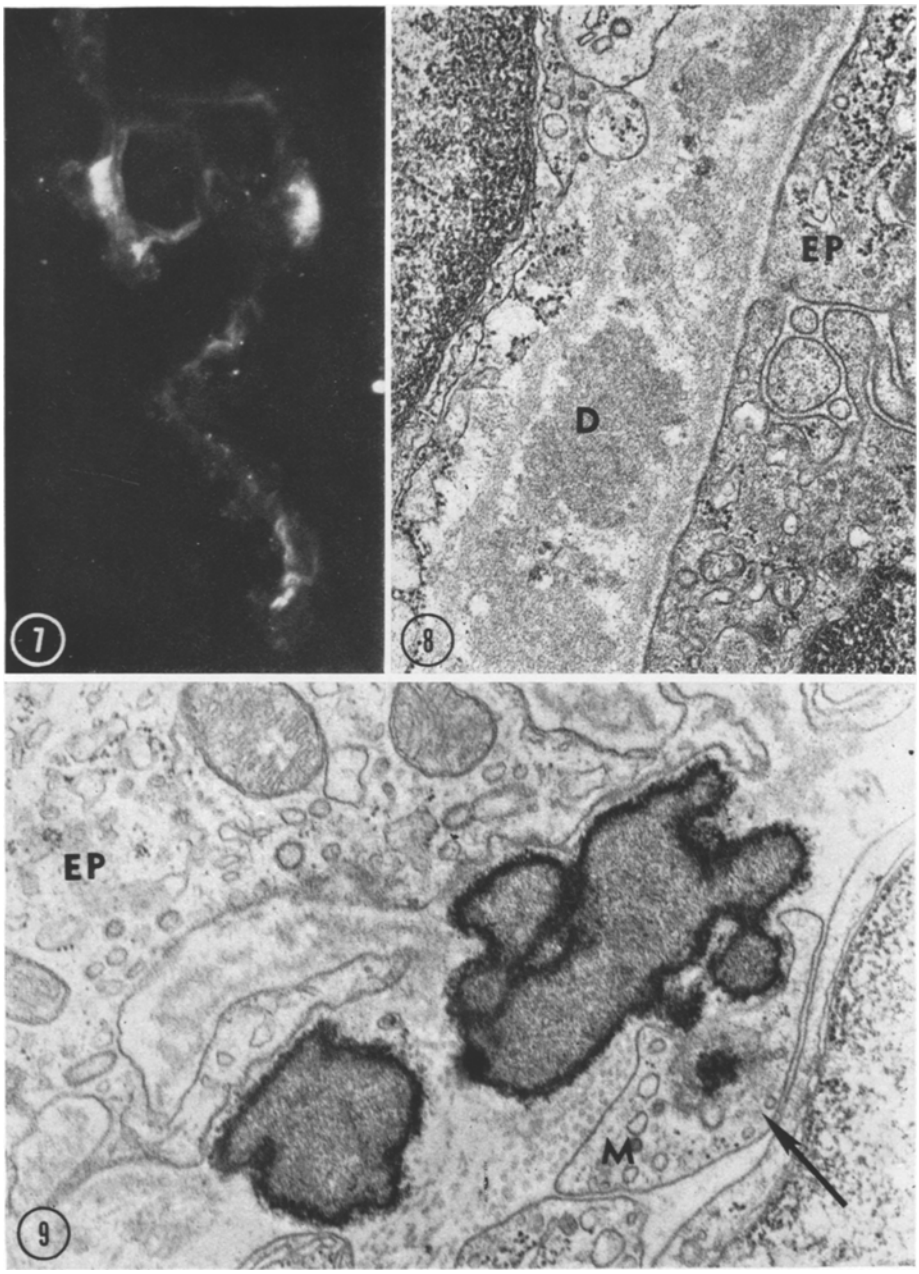


Fig. 7. IgG deposits in the choroid plexus of a 9 month old SWR/J mouse chronically infected with LCM virus. Frozen section stained with fluoresceinated rabbit antibody to mouse IgG. $\times 250$

Fig. 8. Electron dense deposits in the extracellular space next to the basement membrane of an epithelial cell (*EP*) in the choroid plexus of a 9 month old SWR/J mouse chronically infected with LCM virus. $\times 20000$

Fig. 9. Phagocytosis (arrow) of electron dense deposits by a macrophage (*M*) in the perivascular space of the choroid plexus of a 9 month old SWR/J mouse chronically infected with LCM virus. *EP* Epithelial cell. $\times 30000$

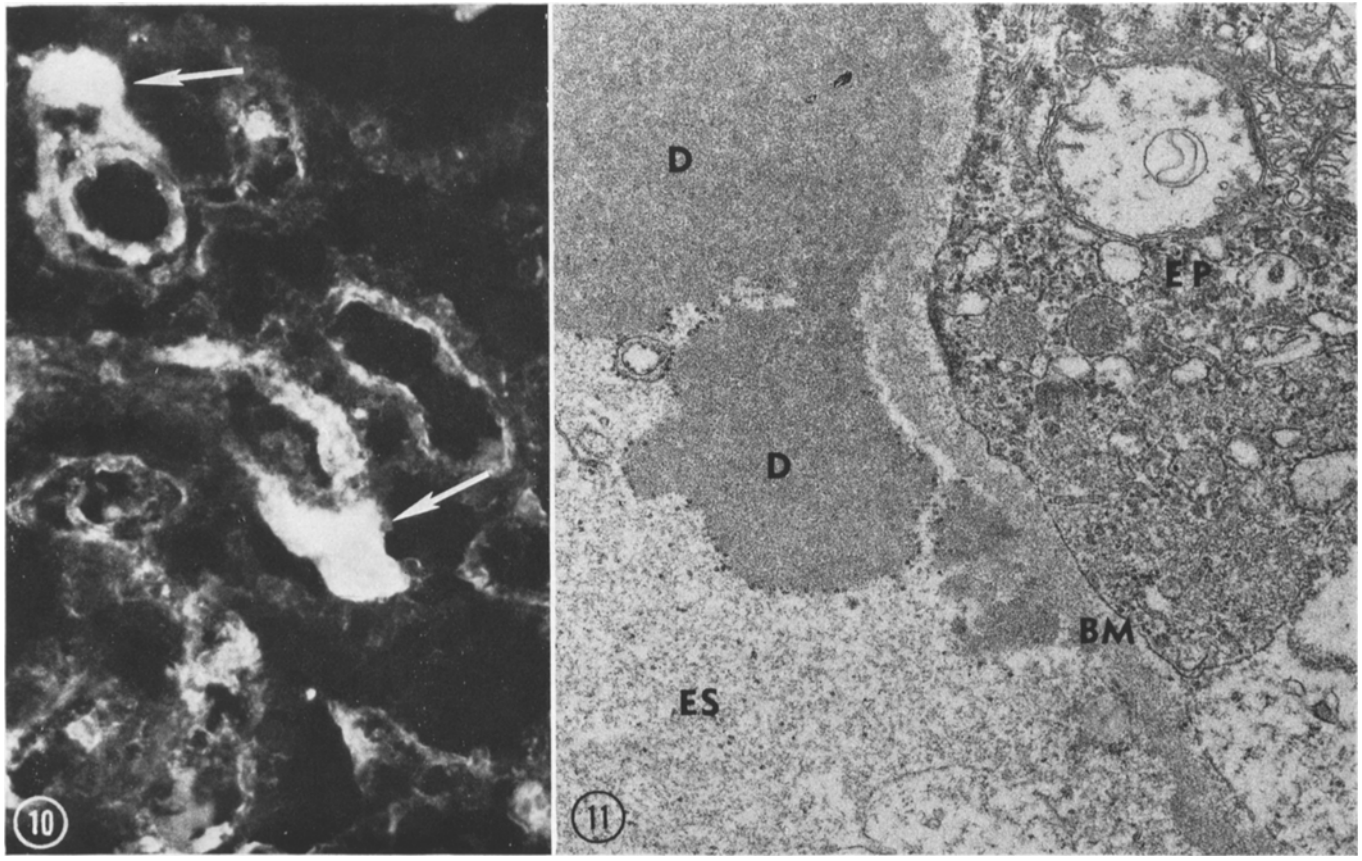


Fig. 10. IgG deposits (arrows) in postmortem human choroid plexus from a patient with SLE. Frozen sections stained with fluoresceinated rabbit antibody to human IgG. × 250

Fig. 11. Electron dense deposits (*D*) attached to the epithelial basement membrane (*BM*) in postmortem choroid plexus of a patient with SLE. *EP* epithelial cell. × 35000

DNA antigen as well as the absence of fibrinogen and albumin indicate entrapment of antigen and antibody complexes rather than nonspecific trapping of serum proteins (Lambert and Dixon, 1968; Cochrane and Koffler, 1973). The presence of DNA antigen in the choroid plexus was established by first eluting the IgG from the tissue section and then staining with fluoresceinated antibody to DNA. Further specificity was seen as DNase treatment of the deposited tissue complex inhibited the above reaction.

Mice inoculated with scrapie agent as well as mice infected *in utero* or at birth with LCM virus harbor these agents for many months usually without clinical signs of disease. The mouse infected with LCM virus, though in antigen excess, produces specific antibodies against LCM virus which combines with virus in the circulation forming virus-antibody complexes. Such complexes are then trapped in the renal glomeruli (Oldstone and Dixon, 1967). As described in this report, mice chronically infected with LCM virus also show granular pattern of IgG, LCM viral antigen(s) and complement but not fibrinogen or albumin in the choroid plexus indicating the presence of immune complex deposits. Owing to both the scattering of deposits in the choroid plexus and limitation of tissue volume we were unable to elute sufficient IgG to determine its immunologic specificity. However, we have little reason to doubt that the deposited IgG is likely to contain specific antibody to LCM virus identical to the complexes in renal glomeruli. In contrast mice infected with scrapie agent fail to show deposits of immunoglobulins in the choroid plexus or brain even in moribund mice with evidence of severe spongiform scrapie encephalopathy. This lack of a detectable host immune reaction in scrapie has been emphasized by others as reviewed by Lampert *et al.* (1972). The fact that scrapie and control mice show some IgG deposits in renal glomeruli is consistent with observations by others who demonstrated that some entrapement of IgG in renal glomeruli is ubiquitous in laboratory mice (Markham *et al.*, 1973) and represents in part deposits of naturally carried oncorna virus-antibody to virus complexes (Oldstone, 1974).

The affected murine choroid plexus usually appears normal by light microscopy indicating that immunofluorescence and electron microscopy are required to detect trapped immune complexes. Using this technic immune complexes are identified by the presence of IgG, C3 and antigen and by the absence of nonspecific trapping of serum proteins such as albumin and fibrinogen. The deposits occur in an irregular, granular pattern in a few patchy areas of the plexus. By electron microscopy the deposits appear as electron dense masses within the extracellular space and attached to the vascular and epithelial basement membrane. In human postmortem choroid plexus such complexes were detected in patients with SLE as described here and previously reported by Atkins *et al.* (1972). Further studies are required to determine the incidence and specificity of immunoglobulin deposits in the choroid plexus of consecutive autopsies particularly in reference to age, viral infections and other autoimmune diseases.

Immune complexes can activate the complement system, release vasoactive substances and induce an inflammatory reaction (Cochrane and Koffler, 1973). Leukocytic infiltrates were observed in the choroid plexus of a few mice chronically infected with LCM virus and also in (NZB $\times$ W) $F_1$ mice immunized with

DNA-m-BSA. Similar infiltrates and IgG deposits have been reported in the choroid plexus of rabbits with acute serum sickness (Koss *et al.*, 1973).

Phagocytosis of the complexes might explain the frequent lack of extracellular, electron dense deposits as observed in mouse and rabbit choroid plexus with leukocytic infiltrates as rapid removal of immune complexes can occur in the presence of macrophages and polymorphonuclear leukocytes (Cochrane and Koffler, 1973). The release of vasoactive substances could affect the tight junctions between the epithelial cells of the choroid plexus which morphologically reflects the blood—spinal fluid barrier (Tennyson and Pappas, 1968). A shift of water, electrolyte and pH balance of the spinal fluid is known to affect animal behavior (Collip, 1920; Huggins and Hastings, 1932) and might also account for transient neurologic and mental disturbances in patients with immune complex disease. Neuropsychiatric disorders occur in 75% of patients with SLE but neuropathologic correlations have often been difficult to establish (Johnson and Richardson, 1968). Immune complexes trapped in the choroid plexus of patients with SLE (Figs. 10, 11) could activate the complement system with the release of vasoactive substances causing permeability disturbances and subsequent spinal fluid changes. Evidence for activation of the complement system with lowering of C4 hemolytic activity in the spinal fluid has been reported in patients with SLE (Petz *et al.*, 1971).

Our studies suggest that the choroid plexus is an important site of immune complex deposits and that this could be responsible for transient neurologic and mental disturbances in patients with SLE, chronic and acute viral infections and other disorders associated with circulating antigen-antibody complexes.

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## References

Atkins, C., Kondon, J., Zuismorio, F., Friou, G.: The choroid plexus in systemic lupus erythematosus. Ann. intern. Med. **76,** 65–72 (1972)

Banks, K., Henson, J., McGuire, T.: Immunologically mediated glomerulonephritis of horses. I. Pathogenesis in persistent infection by EIA virus. Lab. Invest. **26,** 701–707 (1972)

Cochrane, C. G., Koffler, D.: Immune complex disease in experimental animals and man. Advanc. Immunol. **16,** 185–264 (1973)

Collip, J.: The subarachnoid and intra-arterial administration of sodium bicarbonate and other electrolytes. Amer. J. Physiol. **52,** 483–497 (1920)

Dayan, A. P., Stokes, M. I.: Immune complexes and visceral deposits of measles antigen in subacute sclerosing panencephalitis. Brit. med. J. **1972 II,** 374–376

Dixon, F. J., Tonietti, G., Oldstone, M. B. A., Aoki, T., McConahey, P. J.: The effect of chronic viral infection of NZ mice. In: VI International Symp. Immunopathology, ed. P. A. Miescher, p. 377–384. Basel-Stuttgart: Schwabe & Co. Publ. 1971

Hirsch, M., Allison, A., Harvey, J.: Immune complexes in mice infected neonatally with Maloney leukaemogenic and murine sarcoma viruses. Nature (Lond.) **223,** 739–740 (1969)

Huggins, C., Hastings, A: Effect of calcium and citrate injections into cerebral spinal fluid. Proc. Soc. exp. Biol. (N.Y.) **30,** 459–460 (1932)

Johnson, R., Richardson, E.: The neurological manifestations of systemic lupus erythematosus. Medicine (Baltimore) **47,** 337–369 (1968)

Koss, M. N., Chernack, W. J., Griswold, W. R., McIntosh, R. W.: The choroid plexus in acute serum sickness. Arch. Path. **96,** 331–334 (1973)

Lampert, P., Gajdusek, C. D., Gibbs, C. J.: Subacute spongiform virus encephalopathies. Scrapie, Kuru and Creutzfeldt-Jakob disease. Amer. J. Path. **68,** 626–646 (1972)

Lambert, P. H., Dixon, F. J.: Pathogenesis of the glomerulonephritis of NZB/W mice. J. exp. Med. **127,** 507–521 (1968)

Lampert, P. W., Hooks, J., Gibbs, C. J., Gajdusek, D. C.: Altered plasma membranes in experimental scrapie. Acta neuropath. (Berl.) **19,** 81–93 (1971)

Lampert, P. W., Oldstone, M.: Host immunoglobulin and complement deposits in the choroid plexus during spontaneous immune complex disease. Science **180,** 408–410 (1973)

Makojima, T., Gunven, P., Klein, G.: Circulating EBV-associated antigen-antibody complexes in recurrent Burkitt's lymphoma. Nature (Lond.), in press (1974).

Markham, R. V., Sutherland, J. C., Mardiney, M. R.: The ubiquitous occurrance of immune complex localization in the renal glomeruli of normal mice. Lab. Invest. **39,** 111–118, (1973)

Nowoslawski, A., Krawczynski, K., Brzosko, W., Madalinski, K.: Tissue localization of Australian antigen immune complexes in acute and chronic hepatitis and liver cirrhosis. Amer. J. Path. **68,** 31–55, (1972)

Oldstone, M. B. A.: Virus neutralization and virus induced immune complex disease: Virus-antibody union resulting in immunoprotection or immunologic injury—two sides of the same coin. Progr. med. Virol., in press (1974)

Oldstone, M. B. A., Dixon, F. J.: Lymphocytic choriomeningitis: Production of antibody by "tolerant" infected mice. Science **158,** 1193–1194 (1967)

Oldstone, M. B. A., Dixon, F. J.: Lactic dehydrogenase virus-induced immune complex type of glomerulonephritis. J. Immunol. **106,** 1260–1263 (1971)

Oldstone, M., Dixon, F. J.: Inhibition of anti-nuclear and anti-DNA antibody response in New Zealand mice chronically infected with lactic dehydrogenase virus. Science **175,** 784–786 (1972)

Oldstone, M. B. A., Tishon, A., Tonietti, G., Dixon, F. J.: Immune complex disease associated with spontaneous murine leukemia: Incidence and pathogenesis of glomerulonephritis. Clin. Immunol. Immunopath. **1,** 84–93 (1972)

Petz, L., Sharp, G., Cooper, N.: Serum and cerebral spinal fluid complement and serum antibodies in systemic lupus erythematosus. Medicine (Baltimore) **50,** 259–275 (1971)

Porter, D., Larsen, F., Porter, H.: The pathogenesis of Aleutian disease of mink. I. *In vivo* viral replication and the host antibody response to viral antigens. J. exp. Med. **130,** 575–594 (1969)

Porter, D., Porter, H.: Deposition of immune complexes in the kidneys of mice infected with lactic dehydrogenase virus. J. Immunol. **106,** 1264–1266 (1971)

Sun, S., Burch, B., Sohal, R., Chu, K.: Coxsackie B4 viral nephritis in mice and its autoimmune-like phenomena. Proc. Soc. exp. Biol. (N.Y.) **126,** 882–885 (1967)

Tennyson, V., Pappas, G. D.: Choroid plexus In: Pathology of nervous system, vol. 1, ed. J. Minckler, p. 498–518. New York: McGraw Hill 1968

Tonietti, G., Oldstone, M. B. A., Dixon, F. J.: The effect of induced chronic viral infections on the immunologic diseases of New Zealand mice. J. exp. Med. **132,** 89–109 (1970)

Peter W. Lampert, M. D.
Department of Pathology
University of California, San Diego
La Jolla, California 92037/USA