

Acute Serum Sickness Induced Immunologic Injury of the Choroid Plexus; With Particular Reference to the Effect of Prednisolone and the Nature of the Interstitial Cell*

In Joon Choi*, Sang Ho Cho and Dong Sik Kim*

Department of Pathology, Yonsei University College of Medicine, Seoul, Korea

ABSTRACT

Immune complex deposits have been found in the choroid plexus in patients with systemic lupus erythematosus, and it can be assumed that an immune complex injury to the choroid plexus might be related to the neuropsychiatric disorder seen in patients with SLE. Acute serum sickness was experimentally induced in rabbits by intravenous injection of crystalized BSA. Prednisolone in conventional dosage was administered to study the immunologic injury of the choroid plexus as well as the mechanisms involved in the prednisolone effect. Light, electron microscopic and immunofluorescent studies were made. The host immunoglobulins (IgG, IgA, IgM) and beta 1 C globulin were demonstrated in the choroid plexus. Histopathological findings included mild to moderate interstitial and perivascular lymphocyte and plasma cell infiltrations and edema. Control animals showed no immune deposits and no

histopathologic changes. Electron microscopic findings comparing the immunofluorescent and histopathologic changes were minimal, and showed sparse, vague electron dense deposits particularly in the interstitial spaces, knob-like focal thickening of vascular basement membrane, swelling of endothelial cells, and some accentuation of interstitial cells. The morphologic and functional similarities of the choroid plexus and glomerular basement membrane, the findings in morphologic, electron microscopic and immunofluorescent examinations of the experimental rabbits, along with the observed effects of prednisolone, together with similar reports in the recent literature suggest that immunologic injury of the choroid plexus could be considered as a new disease entity. This immunologic injury might play a significant role in neuropsychiatric disorders in the long-standing immune complex deposit diseases. The very interesting finding is the nature and function of the interstitial cell between the endothelial (vascular) and epithelial side basement membranes, and speculation as to whether or not the role of this interstitial cell in choroid plexus injury may be in its possible analogy with glomerular

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mesangial cells.

INTRODUCTION

At present time, experiments support the concept that the choroid plexus is primarily responsible for secretion of cerebrospinal fluid within the ventricular system, as well as the absorptive capacity of these structures. The concept of the choroid plexus subserving transcellular transport of water and solutes is well supported by recent anatomical studies (Davson, 1967; Dohrmann, 1970; Dohrmann, 1971).

The choroid plexus in the ventricles of the brain is composed of vascular membranes of epithelial and endothelial cell types (Maxwell and Pease, 1956). Both the choroid plexus and the glomerular capillary basement membrane have striking morphologic and functional similarities (Maxwell and Pease, 1956; Tennyson and Pappas, 1968). Biochemical similarities have been shown in molecular composition between the glomerular basement membrane and choroid plexus, as well as the alveolar basement membrane, Descemet's membrane, the anterior lens capsule, and Bowman's capsule. Recently Pollay (1974) stated it is clear from the information available that the choroid plexus acts as miniature kidney and, in conjunction with the blood-brain barrier, closely regulates the neuronal environment. Moreover, McIntoch, et al. (1975) proposed that the choroid plexus might be a site of injury or a source of antigen in Goodpasture's syndrome.

Although a large percentage of patients with systemic lupus erythematosus show neurologic and mental aberrations neuropathologic correlation has been difficult (Johnson

and Richardson, 1968). Recently Atkins and co-workers (1972) were the first to report deposits of immunoglobulins in the choroid plexus of two adults having mental disturbances with their systemic lupus erythematosus. Immunological and ultrastructural studies suggest that these deposits are immune complexes and contain DNA antigen. Therefore, it can be assumed that immune complex injury of the choroid plexus might play a role in the neuropsychiatric disorders seen in patients with systemic lupus erythematosus.

Two immunopathologic mechanisms in vascular or glomerular injuries are well known at present time through those of experimental models of glomerulonephritis and human diseases (Dixon, 1968; Germuth and Rodriguez, 1973). In acute, "one shot" serum sickness, a deposit of circulating antigen-antibody complexes is found on vascular membranes. This produces inflammatory changes in the kidneys, heart, arteries, and joints. The functional and structural similarities between the glomerular basement membrane and the choroid plexus suggest that antigen-antibody complexes might subject the choroid plexus to the same type of injury as the glomerular capillaries.

The present study, therefore, is designed to induce an immunologic injury of the choroid plexus using acute serum sickness, and to define the mechanism involved in the effect of prednisolone on the choroid plexus lesion due to immunologic injury.

MATERIALS AND METHODS

A. Materials

A total of nineteen albino rabbits weighing approximately 2 kg. each were used. Crysta-

lized Bovine Serum Albumin (BSA) from the Miles Laboratory was used for the induction of "one shot" acute serum sickness. A total of 10 gm. of crystalized BSA contained in 100 ml. phosphate buffered saline was processed by membrane filtration after autoclaving. A high-titered rabbit anti-BSA serum was used to produce the daily capillary precipitation reactions. Prednisolone from the Dong Sin Laboratory was used to produce the anti-inflammatory and anti-immunologic effects.

B. Methods

The animals for the experiment were divided into three groups; Group I was normal control, 5 rabbits; Group II was the experimental group, 9 rabbits; and Group III was phosphate buffered saline control group, 5 rabbits. Group II was subdivided into A and B. The subgroup A was an experimental control 4 rabbits; B was the prednisolone-treated group, 5 rabbits. These nine rabbits in experimental group II were injected intravenously with 0.5 gm. crystalized BSA in 5 ml. phosphate buffered saline. Beginning on the fourth day and continuing daily thereafter, the 5 rabbits of subgroup B were given 1.5 mg. per kg. of prednisolone intramuscularly. In all rabbits clearance of BSA from the circulation was checked by daily capillary precipitation reactions using high-titered rabbit anti-BSA serum (Germuth, F. G., Jr., et al., 1957). Unilateral nephrectomy for the confirmation of glomerular lesions was done on the day of maximum BSA clearance. After three to a maximum of five days after complete or maximum BSA clearance, all animals were sacrificed on the twenty-first and second experimental day. For immunofluores-

cent examination the tissues of the choroid plexus were immediately frozen in dry-ice-acetone mixture and cut in three to four micron thickness. The sections were examined by a direct immunofluorescent antibody technique with specific fluorescent-tagged antisera fractions, such as FITC-conjugated anti-rabbit immunoglobulins (IgG, IgA, IgM), anti-rabbit beta 1 C globulin and rabbit anti-BSA.

The tissues of the choroid plexus for histopathologic examinations were stained with hematoxylin and eosin, and with the periodic acid Schiff technique. Ultrastructural examination with usual processing and double staining methods was done using Hitachi HU-11E Electron Microscope.

RESULTS

In the experimental control group maximum BSA clearance showed in 3 rabbits on the 15th and 16th day and in the prednisolone-treated group, one rabbit on the 16th day and 4 rabbits on 17th and 18th days. These findings indicated delayed antigenic clearance particularly in the prednisolone-treated group.

Granular deposits of immunoglobulins (IgG, IgA, IgM) and beta 1 C globulin were localized in the glomerular capillary loops of all of the experimental control animals (II-A), and were localized mainly in the glomerular mesangium of all prednisolone-treated animals (II-B). Histopathological examination of the kidneys from these animals showed moderate to marked proliferative and exudative glomerulonephritis in the experimental control group, but only minimal lesions in the prednisolone-treated group. These findings were almost similar both in the nephrectomized and sacrificed kidneys.

Table 1. Light Microscopic and Immunofluorescent Findings

Groups & Rabbit No.	Maximum BSA Clearance (days)	Sacrificed (days)	Histopathology					Immunofluorescence		
			epithelium vacuolation	lymph.	stroma plasma cell	capillary edema	capillary wall thick	Immunog.	C ₃	BSA
A	1	15	+	++ (focal)	+	++	-	+	±	-
	4	16	++	+	± (focal)	++	-	++	+	-
	5	19	±to+	++ (diffuse)	+	+	-to±	++	+	-
	7	16	+	++ (focal)	+	+	-to±	##	+	-
B	10	17	++	±	±	±to+	-	±	±	-
	11	17	##	±	±	±to+	-	±	±	-
	12	18	++	±	±	±to+	-	+	+	-
	15	17	17*	+	±	±	±	-	±	±
	18	16	21	++	-to±	±	±	-	+	+
T	34		##							
	35		++							
	36		##							
	37		++							
	39		##							
III	16		##							
	27		++							
	28		+							
	29		+							
	30		##							

* Immediate sacrifice after needle biopsy

Light and immunofluorescent microscopic findings of the choroid plexus are summarized in the Table 1. Granular deposits of immunoglobulins and beta 1 C globulin were demonstrated on the choroid plexus by immunofluorescent examination. BSA was no longer demonstrated on the choroid plexus, although it was found, to a lesser extent, in the glomeruli of the nephrectomized kidneys. The immune deposits appear to be localized in the basement membrane and in the interstitial areas (Fig. 4, 5, 6, & 7). Light micro-

scopic examination of the choroid plexus of the experimental control group showed minimal to moderate cellular infiltration, particularly focally in the perivascular and interstitial areas (Fig. 1, 2, & 3), except one rather diffuse infiltration in one rabbit (No. 11-A-5). The infiltrated cells were mainly lymphocytes, occasionally plasma cells and rarely polymorphonuclear leukocytes. Histopathologic examination of the prednisolone-treated group showed a minimal degree of focal cellular infiltration and interstitial

edema. Sometimes some impressively accentuated interstitial cells were found. The vascular basement membrane by periodic-acid Schiff stain appeared to be normal in thickness. Neither histopathologic abnormalities nor immune deposits were seen in the kidneys and the choroid plexus of groups I and II.

Electron microscopic examination of the normal control (group I) and phosphate buffered saline control (group III) group showed quite similar findings. There were (Fig. 8) mitochondrial rich epithelial cells with numerous surface microvilli and secretory vacuoles. The interstitial space was rather narrow, loose in texture, containing collagen and variable sized capillaries. The interstitial space was bordered by epithelial side and endothelial side (vascular) basement membranes, and has interstitial cells which were located either in the perivascular or interstitial areas. The interstitial cells had a small number of cytoplasmic organelles. Endothelium was present in the vascular lining.

The findings of the experimental control (group II-A) (Fig. 9, 10, & 11) showed some focal knob-like thickenings, irregular folds and focal splitting of the endothelial side basement membrane, around which vague, slightly electron dense, materials were found. The interstitial spaces were markedly widened and appeared edematous. Interstitial cells were prominent or appeared to be accentuated. Some of the interstitial cells contain proteinous material in their cytoplasm. In the interstitial spaces, vague, slightly electron dense, proteinous-like materials were occasionally found. Some of the interstitial cells showed abundant cytoplasm with markedly dilated cisterna, which were adjacent

to the vascular basement membrane.

The findings of the prednisolone-treated experimental group (II-B) (Fig. 12) showed less edematous or narrow interstitial spaces with prominent and accentuated interstitial cells. In the interstitial spaces, occasionally vague slightly electron dense materials were seen. Protrusion of the perivascular interstitial cells into the vascular lumen was impressive (Fig. 12). The vascular basement membrane showed occasional knob-like focal thickening and some irregularity. The endothelial cells were swollen.

Although no obvious or characteristic electron dense deposits were found, the vague, slightly electron dense deposited materials around the vascular basement membrane and interstitial spaces might be the same type of deposits as those seen by immunofluorescent examination to be specific for immunoglobulins and beta 1 C globulin.

DISCUSSION

The neuropsychiatric symptoms or complaints in patients with systemic lupus erythematosus (SLE) are about 59% (Estes and Christian, 1971), 75% (Johnson and Richardson, 1968), and about similar frequency (Greenhouse, 1968; Duboids, et al. 1973). There also are reports of a high degree of correlation between positive neurologic symptoms and positive brain scans (Bennahum, et al., 1974), and of 2 cases of SLE with chorea (Mitudome, et al., 1974). A few reports have been found of immunoglobulins and C3 deposits in the choroid plexus in human SLE (Atkins, et al., 1972; Sher and Pertschuk, 1974), and in rabbits (Koss, et al., 1973) and also spontaneously in NZB hybrid mice (Lampert and Oldstone, 1973),

and also found of the lowered complement in the cerebrospinal fluid of patients with C.N.S. lupus (Petz, et. al., 1971).

Immunologic injury to various tissues may occur through antigen-antibody reactions either with or without complement mediation. Immunopathogenetic mechanisms in vascular injury were first defined in experimental models of glomerulitis. These various experimental models of human glomerulonephritis fit into two general immunopathogenetic mechanisms each depend upon the action of circulating antibodies (Dixon, 1968; Germuth and Rodriguez, 1973). The first of these is known as anti-glomerular basement membrane disease and involves antibodies to glomerular basement membrane or chemically and immunologically similar structures. The second depends upon the formation of circulating antigen-antibody complexes, some of which become trapped in the glomeruli causing glomerulonephritis. The first suggestion that circulating immune complexes might cause glomerulonephritis came from the studies of "one shot" serum sickness (Von Pirquet, 1911). In "one shot" serum sickness, introduction of a foreign protein induces antigen-antibody complexes in the circulation. These may be deposited on vascular membranes and produce inflammatory changes in the kidneys, heart, arteries, and joints, findings which are similar to the several diseases in man, such as glomerulonephritis, SLE, and rheumatoid arthritis (Cochrane & Dixon, 1969). Experimental studies on the BSA-rabbit system indicate that the immune complex size is normally the major determinant for site of localization of circulating complexes within the glomerulus as well as of the nature of the glomerular

lesions. The site of localization of the complexes, rather than their size in the circulation, determines the diffuse or focal nature of the glomerular lesion (Germuth and Rodriguez, 1973). The role of the complement and other mediators or factors by antigen-antibody complexes have been extensively studied in various experimental models (Dixon, 1965; Cochrane and Dixon, 1969; Germuth and Rodriguez, 1973).

The morphological structure (Maxwell and Pease, 1956) as well as biochemical compositions of the choroid plexus (Kefalides and Denuduchis, 1969) is very similar to that of the renal glomerulus. Functionally both act as a filter with a functional similarity (Tennyson and Pappas, 1968; Pollay, 1974). Therefore, because of these functional and morphological similarities between the glomerular basement membrane and the choroid plexus, it can be assumed that the choroid plexus could be subjected to the same type of immunologic injury depend on the action of circulating antibodies

By immunofluorescent examination of the choroid plexus following acute serum sickness, immunoglobulins and beta 1 C globulin were localized particularly in the vascular basement membrane and in the interstitial areas. The inflammatory changes of the interstitial areas by histopathologic examination were very similar to the glomerular lesions as well as other vascular lesions of the body. Although definite or obvious electron dense deposits were not identified in the choroid plexus basement membrane and in the interstitial areas, by electron microscopic examination the sparse, vague, slightly electron dense material deposits might be counterpart deposits to the host immunoglobu-

lins and beta 1C globulin.

In the experimental control group, the inflammatory changes, immune deposits by immunofluorescent technique, and sparse slightly electron dense deposits by the electron microscopic study were rather greater than those found in the prednisolone-treated group. By electron microscopic examination, because there were no definite electron dense deposits identified neither in the experimental control nor in prednisolone-treated groups, no definite or plausible mechanisms for the immunosuppressive effect of prednisolone can be proposed. However, it can be considered and be possible that reoriented specific macromolecules due to prednisolone, of preformed Class I immune aggregates, may be interrupted in crossing the endothelial side vascular basement membrane and thus some inflammatory reaction could have been prevented. This interpretation is the same as that given in experimental studies of glomerular injury (Germuth and Rodriguez, 1973; Lee, et al., 1974). In addition, corticosteroids may inhibit immune responses by specifically interfering with the pre-induction period; antigen-reactive cells, and antigen-handling system (Craddock, et al., 1967; Dukor and Dietrich, 1967).

In our experimental study especially interesting findings were the accentuation of interstitial cells more so in the prednisolone-treated group than in the experimental control group, as well as prominent protrusion of interstitial cells into the vascular lumen. In the glomerular lesion of the acute serum sickness induced rabbits, partial or transient mesangial interposition was seen electron microscopically and mesangial immune dep-

osits were identified (Lee, et al., 1974). The effect of corticosteroids on phagocytosis by macrophages is thought to be biphasic; small doses stimulate and large doses depress phagocytosis (Snell, 1960; Vernon-Roberts, 1969). Therefore, one of the possible mechanisms of action of steroids may be to directly stimulate the phagocytic function of the mesangial cells (?) (Vernier, et al., 1971). For these reasons, the findings of some accentuation of the interstitial cells of the choroid plexus, particularly so in the prednisolone-treated group, suggests that the nature and function of the interstitial cells of the choroid plexus may be analogous to the glomerular mesangial cell.

Bjorneboe and Prytz (1975) proposed a hypothesis about the function of Kupffer cells and the pathogenesis of cirrhosis of the liver. This hypothesis is also interesting in its possible analogy to the kidney. The function of the Kupffer cell may be similar to that of the glomerular mesangial cell in that both may remove toxic materials before damage to the organ occurs. A failure to remove such toxic materials or the presence of immune deposits in glomerular lesions may represent some blockage in the reticuloendothelial system or, more particularly, in the mesangial cell, or Kupffer cell. The role of the factors of macrophage receptors and immune-complex composition is unknown in renal diseases. However, a trial of some reticuloendothelial stimulant might be benefit for the renal lesions with more a failure to remove such as mesangiocapillary glomerulonephritis and diffuse disseminated lupus mesangiopathic glomerulonephritis, and cirrhosis (?) probably due to a failure of Kupffer cell function. For these reasons, we

speculate that a failure of the interstitial cells of the choroid plexus might cause neuropsychiatric disorders.

This hypothesis assumes that immune complex injury to the choroid plexus might play a significant role in the neuropsychiatric disorders and could be considered as a new disease entity. Immunofluorescent studies might well help to elucidate the pathogenesis underlying the clinical syndromes not only of "lupus cerebritis" but also "neurologic and mental aberrations" seen in cases of longstanding circulating immune complex deposit diseases. Further studies of these important concepts will add significantly to the understanding of the nature and function of the interstitial cells of the choroid plexus and to our understanding of the pathogenesis of cerebritis in longstanding immune deposit diseases.

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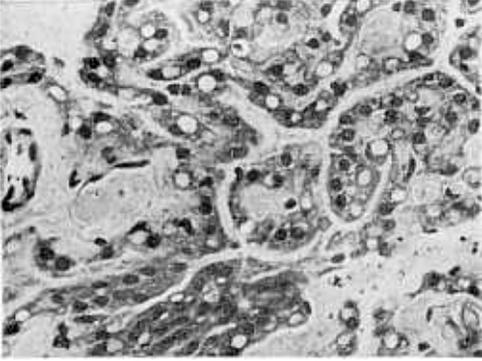


Figure 1. Choroid plexus of normal control. Choroid plexus lined by moderately vacuolated epithelial cell and loose interstitial spaces with endothelial lined vascular structure. Animal No. I-36 H-E stain. 430×

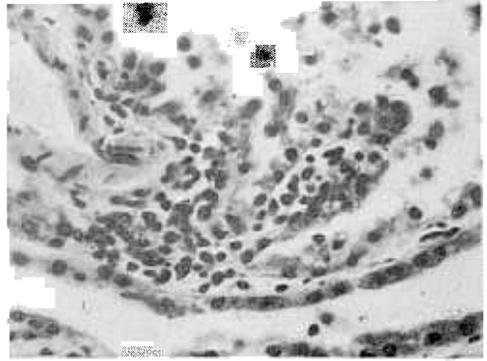


Figure 2. Choroid plexus of experimental control. The interstitial tissue is infiltrated with lymphocytes and plasma cells. The epithelial vacuolation is occasionally reduced. Animal No. II-A-7 H-E stain. 430×

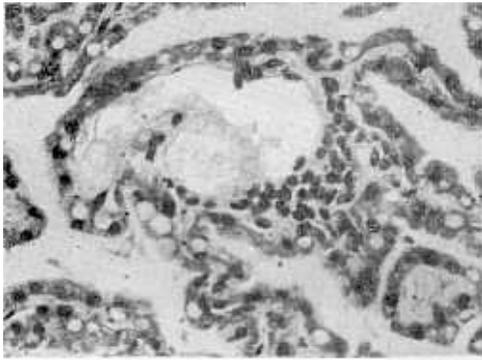


Figure 3. Choroid plexus of prednisolone-treated rabbit. Cellular infiltration is decreased, but focal collections are still present. Some prominent interstitial cells are seen. Epithelial vacuolation is fairly similar to that of the normal control. Animal No. II-B-18 H-E stain, 430×



Figure 4. Choroid plexus of experimental control. Immunofluorescent examination shows prominent $\#$ intensity granular deposits of host immunoglobulins mainly in the interstitial spaces. Animal No. II-A-7 Immunoglobulins 430×



Figure 5. Choroid plexus of experimental control. Immunofluorescent examination shows $+$ intensity granular deposits of host C_3 in the vascular wall and interstitial spaces. Animal No. II-A-7 Beta 1 C globulin (C_3) 430×



Figure 6. Choroid plexus of prednisolone-treated rabbit. Immunofluorescent examination shows $+$ intensity granular deposits of host immunoglobulins in the interstitial spaces and vascular wall. Animal No. II-B-18 Immunoglobulins 430×

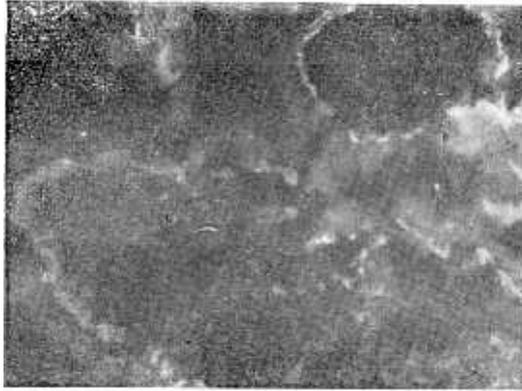


Figure 7. Choroid plexus of prednisolone-treated rabbit. Immunofluorescent examination shows +intensity granular deposits of host beta 1 C globulin mainly in the vascular wall and some in the interstitial spaces. Animal No. I-B-12 Beta 1C globulin(C3) 430×

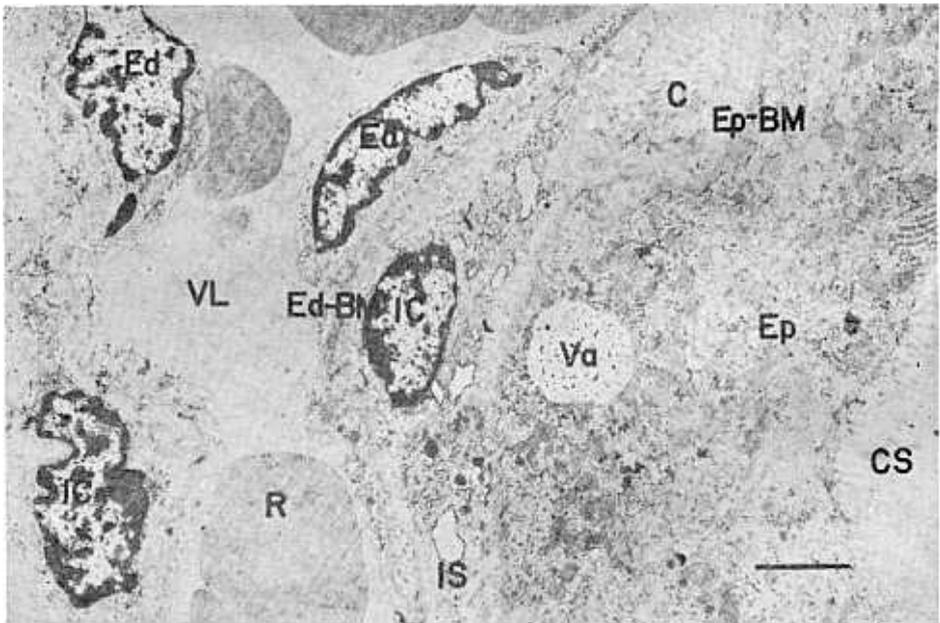


Figure 8. E. M. of choroid plexus of normal control. The micrograph shows cerebrospinal space (CS), epithelial lining (Ep), epithelial vacuole (Va), epithelial side basement membrane (Ep-BM), collagen (C), interstitial space (IS), interstitial cell (IC), endothelial side basement membrane (Ed-BM), endothelium (Ed), vascular lumen (VL), and red blood cells (R). Animal No. I-36 16,000×

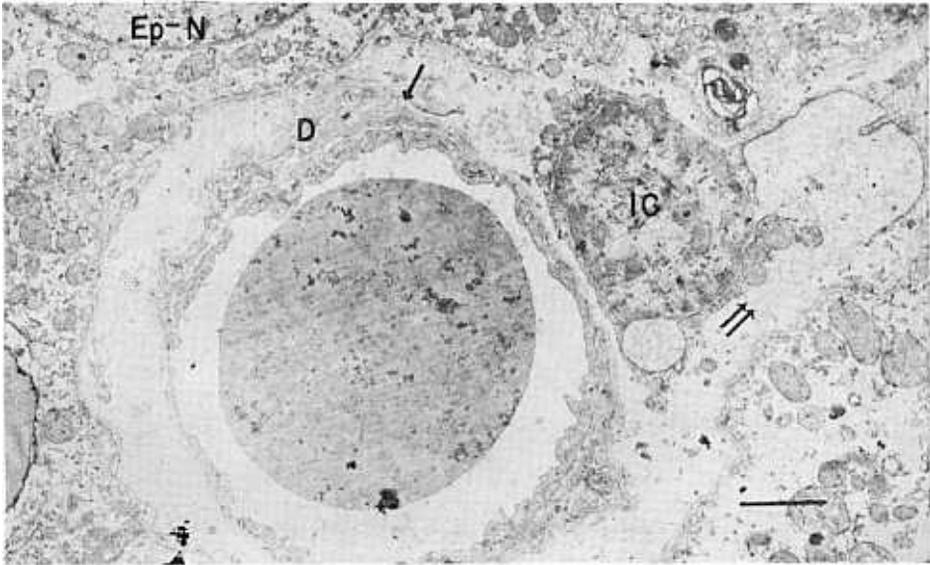


Figure 9. E. M. of choroid plexus of experimental control. The micrograph shows small capillary containing RBC. The endothelial side basement membrane shows focal knob-like thickening, focal irregular splitting (↑) with surrounding vague electron dense material deposits(D). The perivascular interstitial cell (IC) shows some accentuation engulfing some proteinous materials with focally defected cytoplasmic borders(⇓). The epithelial cell nucleus(Ep-N) is seen. Animal No. II-A-7 16,000×

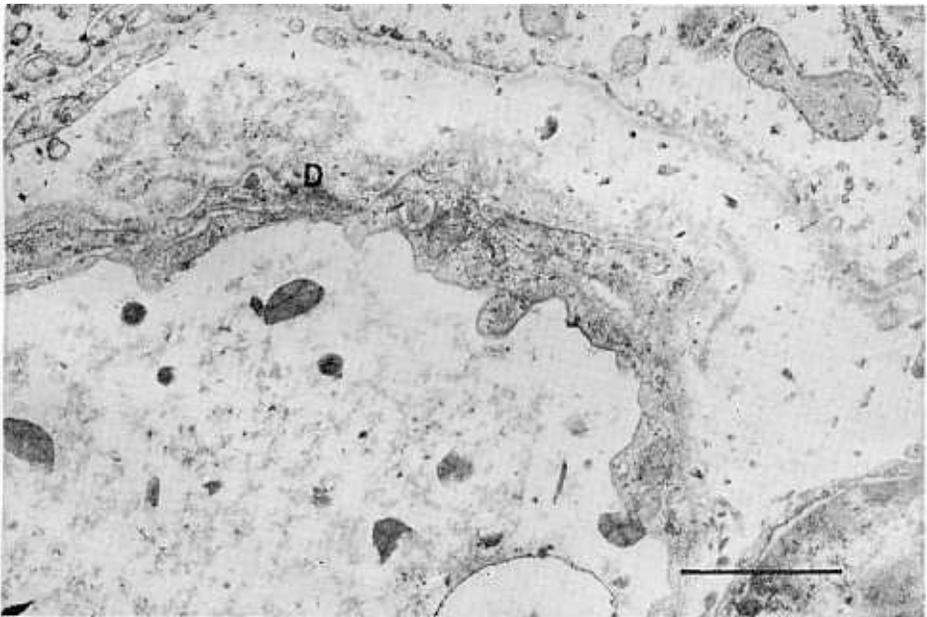


Figure 10. E. M. of choroid plexus of experimental control. The micrograph shows focal cauliflower-like irregular folding and splitting of the endothelial side basement membrane with surrounding vague electron dense deposits (D). Animal No. II-A-7 30,000×

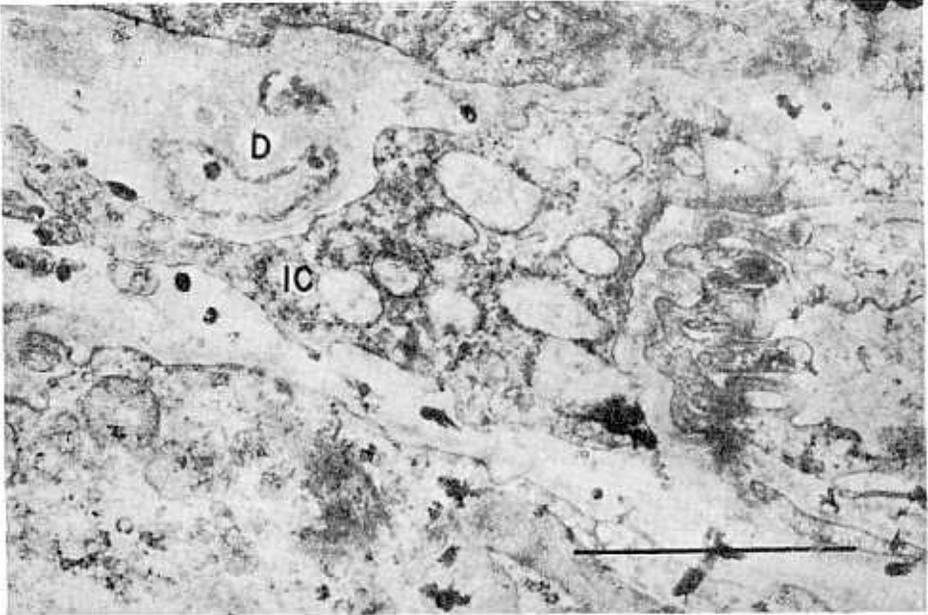


Figure 11. E.M. of choroid plexus of experimental control. The micrograph shows irregular swelling of endothelial cells, irregular foldings of the endothelial side basement membrane adjacent interstitial cell (IC) with dilated cisterna, and obvious electron dense materials (D) in the interstitial space. Animal No. II-A-1 50,000 \times

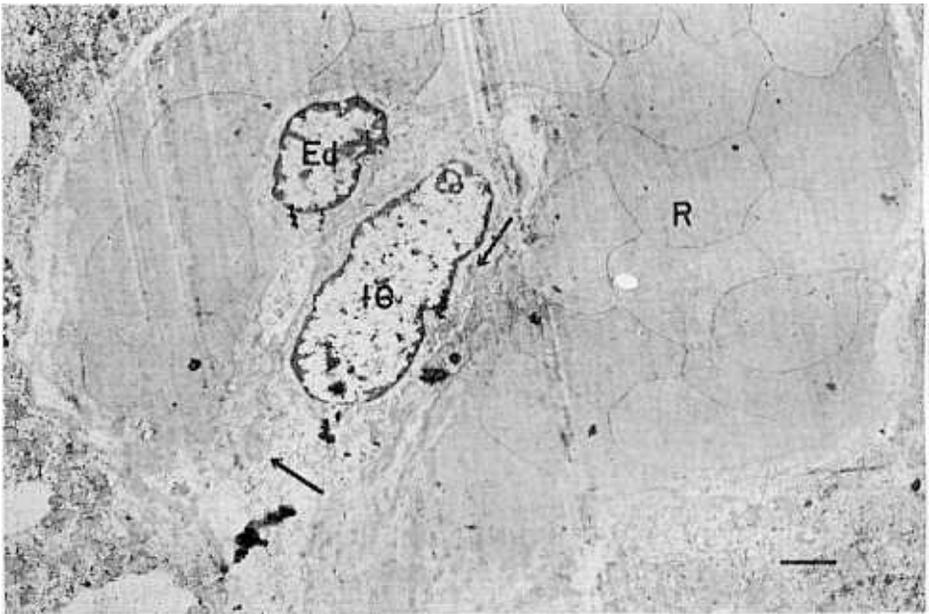


Figure 12. E.M. of choroid plexus of prednisolone-treated rabbit. The micrograph shows focal irregular foldings and knob-like thickening of the endothelial side basement membrane (\uparrow), marked endothelial swelling (Ed), and impressive protrusion of interstitial cells (IC) and interstitial tissue into the vascular lumen, with accentuation of interstitial cells. Animal No. II-B-18 8,250 \times