A Quantitative Light- and Electron-Microscopic Study of Type IV Nuclear Bodies in Crescentic Glomerulonephritis

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Type IV nuclear bodies were found in all renal biopsies obtained from 14 patients with crescentic glomerulonephritis (CGN) and in 8 of 43 control patients studied by light and electron microscopy. The mean ratio of Type IV nuclear bodies per 100 tubular cross-sections examined was 0.67±0.27 for the CGN cases, which was significantly different from 0.09±0.26 obtained for the controls ($P < 0.05$). Type IV nuclear bodies were most commonly seen in the epithelial cells of proximal tubules but were also seen occasionally in interstitial fibroblasts and cells of a collecting duct and a developing crescent. (Am J Pathol 1981, 102:359–366)

NUCLEAR BODIES were originally described by de Thé et al[1] and their patterns first defined by Bouteille et al,[2] who classified them into five types. Early reports of their occurrence[3,4] did not distinguish precisely between the morphologic configurations of such nuclear bodies (also termed "sphaeridia" in the European literature), nor was any pathognomonic significance attached to them. However, it became evident with time that, while the different forms appear to represent developmental phases of a single fundamental process, Type III–V (complex) nuclear bodies are more often seen in pathologic processes, whereas Types I and II (simple) nuclear bodies are commonly seen in normal tissue under varying physiologic conditions.[5] Further, Type IV nuclear bodies are frequently associated with proven or suspected virus-induced disease, specifically cell lines infected with SV40 virus,[6,7] cases of subacute sclerosing encephalitis,[8,9,10] Argentine hemorrhagic fever,[11] and Creutzfeldt-Jakob disease.[12] Iwasaki et al[13] identified paramyxovirus-like nucleocapsids in nuclear bodies isolated from brain cells derived from cases of multiple sclerosis.

Reports of an association between renal disease and nuclear bodies are uncommon. Simple nuclear bodies were described by Runeburg et al[14] in a hypomagnesemic patient with glomerular and tubular basement membrane immune complexes detected by renal biopsy. "Light" nuclear bodies, generally of simpler type, were seen by Collan and Lähdevirta[15] in renal biopsies from 18 patients with nephropathia epidemica. In 1976, nuclear bodies were reported in renal tubular epithelial cells in a case of Wegener's granulomatosis.[16]

We report the ubiquitous finding of Type IV nuclear bodies in renal biopsies obtained from patients with crescentic glomerulonephritis (CGN). A possible viral etiology for idiopathic CGN is discussed.

Materials and Methods

Clinical Cases

Specimens were derived from renal biopsy and autopsy material obtained from 1977 to 1979 from the University of Arizona Health Sciences Center and the Veterans Administration Medical Center, Tucson, Arizona. There were fourteen cases of CGN characterized by involvement of greater than 50% of glomeruli with cellular and/or collagenized crescents within Bowman's space in a renal specimen adequate for evaluation. All had tissue for light- and electron-microscopic examination, and 12 had tissue for immunofluorescence. Forty-three noncrescentic GN control cases were examined, representing other mechanisms of renal dysfunction (glomerular, tubular, and vascular), for whom diagnosis had been previously established on the basis of light-microscopic, immunofluorescence, and/or electron-microscopic examination.

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Light Microscopy

Tissue for light microscopy was fixed in 10% neutral buffered formalin and routinely processed. Sections were cut at 3 μ and stained with hematoxylin and eosin, periodic acid–Schiff (PAS), trichrome, and Jones silver stains.

Tissue evaluated for the presence and frequency of nuclear bodies was prepared according to the methods given for electron-microscopic examination. One-micron toluidine-blue-stained epoxy sections from 3–8 different blocks of tissue were examined by light microscopy from each of 43 control cases and 14 CGN cases, and the total number of nuclear bodies scored.

Immunofluorescence

Tissue for immunofluorescence was immersed in OCT mounting medium (Lab-Tek Products, Naperville, Ind), snap-frozen in isopentane chilled in liquid nitrogen, and cut at 6–8 μ in a cryostat. The sections were fixed in acetone for 5 minutes, rinsed in phosphate-buffered saline for five minutes, and treated with antihuman IgA, IgG, IgM, C3, C4, fibrinogen and albumin (Cappel Laboratories, Cochranville, Pa) for 30 minutes. They were then rinsed three times over a total time period of 6 minutes and coverslipped with Gelvatol as a mounting medium (Monsanto, Indian Orchard, Mass). They were examined using a Zeiss epi-illumination ultraviolet microscope employing BP 450–490 and KP 560 filters.

Electron Microscopy

Tissue for electron microscopy was fixed for 2 hours in 3% glutaraldehyde made up in 0.1 M phosphate buffer (pH 7.2), postfixed in 1% osmium tetroxide for 90 minutes, dehydrated in a graded series of ethanol, and embedded in Spurr's epoxy resin. One-micron sections were cut on a Sorvall MT2-B ultramicrotome and stained with toluidine blue. Selected blocks were thin-sectioned with a du Pont diamond knife, stained with lead citrate and uranyl acetate and examined under a Hitachi HU-12 electron microscope. Fifteen control cases and fourteen CGN cases were examined under the electron microscope, and the number of nuclear bodies present was determined.

Statistical Analysis

The frequency of nuclear body formation in the CGN group and the noncrescentic GN control group were compared by the use of standard methods for statistical analysis.

Results

Clinical Cases

The patients with crescentic glomerulonephritis ranged in age from 8 to 68 years (8 males, 6 females). Two had ASO titers of 1:500 and 1:600, obtained 7 months and 1 month prior to biopsy, respectively, and 1 had an ANA titer of 1:320 in a rim pattern without other signs or symptoms of systemic lupus erythematosus. Serologic studies were negative in the remaining patients. Ten of the patients had symptomatology of infection or inflammatory disease sometime within the year preceding the development of renal insufficiency. Nine had had infections: of these, 6 were upper respiratory (including 2 cases of otitis media) or pneumonic in character, occurring 4–7 months before renal biopsy, 1 was associated with extensive burns 1 year before biopsy, 1 was a perinephric abscess 3 months before biopsy, and 1 patient had documented pyelonephritis 1 month before biopsy. The tenth patient had a multisystem vasculitis, which was not further characterized and which accompanied signs of renal deterioration. Among these 10 patients, 4 also gave histories of migratory arthralgias or myalgias ranging in duration from 4 months to several years preceding acute decline in renal function. Serum creatinines ranged from 3 to 14 mg/100 ml. Urinalysis in all cases revealed proteinuria and hematuria; red blood cell casts were identified in 7 cases and white blood cells and/or casts in 4. Urine protein quantitation, performed in 4 cases, demonstrated 620 mg to 13 g of protein per 24 hours.

Routine Pathologic Evaluation

Light Microscopy

All 14 patients had renal tissue adequate for evaluation. Patients with CGN had from 6 to 55 glomeruli present on biopsy; 3 had open biopsies with more than 50 glomeruli. All of these has a minimum of 50% of glomeruli involved with crescents in cellular or collagenized phases (Figure 1). Two of the specimens demonstrated diffuse hypercellularity intrinsic to the glomerular tuft itself (in addition to the extracapillary cellularity of the crescent); two others had focal, segmental areas of intrinsic tuft necrosis. In all cases, there was extensive tubular cellular injury and evidence of regeneration, with numerous hyaline and cellular casts. The interstitium was edematous and showed early fibrosis manifested by collagen rich in mucopolysaccharides. Interstitial inflammatory infiltrates composed of polymorphonuclear leukocytes, lymphocytes, and plasma cells were moderate to marked in severity. There was no evidence of vasculi-

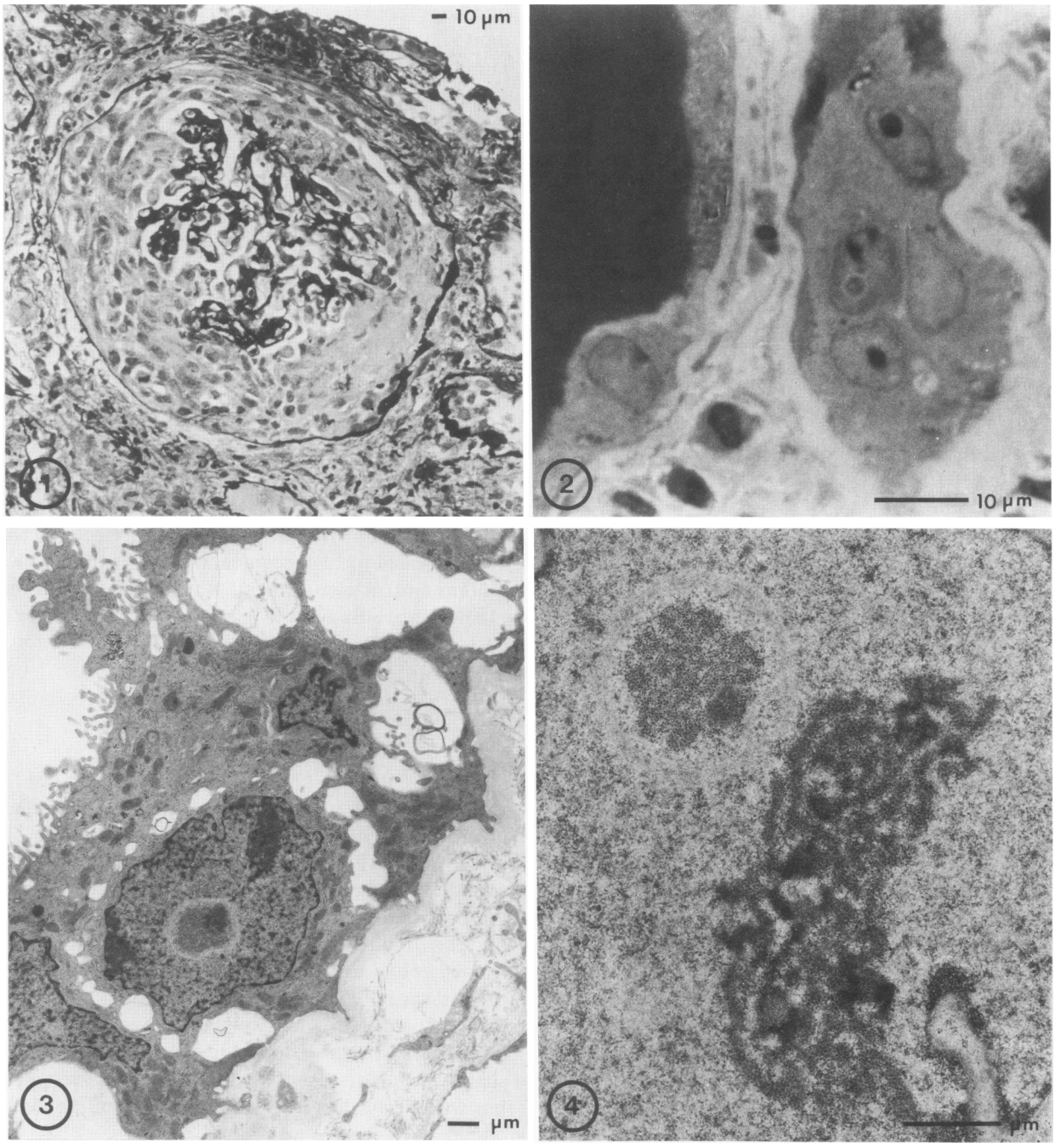

Figure 1—Light micrograph of renal tissue obtained from a patient with crescentic glomerulonephritis. The cross-sectional area of the glomerular capillary tuft has been markedly reduced by the proliferating cellular crescent. (Jones silver stain, ×265) **Figure 2**—Light micrograph of epoxy-embedded renal tissue from a patient with crescentic glomerulonephritis. A Type IV nuclear body characterized by a dense core surrounded by a clear halo is evident in one of the tubular epithelial cells. (Toluidine blue, ×1700) **Figure 3**—Low magnification electron micrograph of a proximal tubule from a patient with crescentic glomerulonephritis showing a typical Type IV nuclear body near the center of the nucleus. The loss of surface microvilli, widened intercellular spaces, and a thickened basement membrane are evidence of nonspecific tubular injury. (Lead citrate and uranyl acetate, ×5800) **Figure 4**—Higher-power electron micrograph of a tubular epithelial cell showing a Type IV nuclear body (*upper left*) and a prominent nucleolus (*lower right*). The Type IV nuclear body can be seen to consist of a granular center surrounded by a microfibrillar cortex. The nucleolus shows a well-developed nucleolonemata and an inconspicuous pars amorpha. (Lead citrate and uranyl acetate, ×17,700)

tis, including the biopsy from the patient with multisystem evidence of vasculitis elsewhere. The remaining 9 cases had no intrinsic morphologic abnormality of the glomerulus except for the crescent formation.

A summary of the patterns of renal disease exhibited by control patients is presented in Table 1. Seventeen of the 43 control patients had a principally glomerular process: 4 had diffuse proliferative or membranous variants of systemic lupus erythematosus nephritis, 3 had acute proliferative or necrotizing GN,

Table 1—Distribution of Control Patients by Diagnosis

Glomerular:	17
Diffuse proliferative or membranous GN of SLE (4)	
Acute proliferative or necrotizing GN (3)	
Mesangial proliferative GN (5)	
Idiopathic membranous GN (4)	
Diabetic glomerulosclerosis, diffuse (1)	
Tubulointerstitial:	8
Chronic (1)	
Acute or subacute (6)	
Granulomatous (1)	
Tubular:	5
Acute tubular necrosis (1)	
Acute pyelonephritis (3)	
Tubular nephrocalcinosis (1)	
Vascular:	10
Benign nephrosclerosis (7)	
Malignant nephrosclerosis (1)	
Vasculitis (2)	
Allograft rejection:	2
Chronic (1)	
Acute and chronic (1)	
End-stage renal disease:	1

5 had mesangial proliferative GN, 4 had idiopathic membranous GN, and 1 had diabetic glomerulosclerosis. Among these patients with primary glomerular disease, eight had significant associated tubular injury, inflammation, and/or evidence of regeneration. Eight additional control patients had a combined tubulointerstitial nephritis. One was chronic (with interstitial fibrosis), 6 were acute or subacute (including 1 case with a prominent eosinophilic component suggesting an allergic etiology), and 1 was granulomatous. There were 5 control cases with primary tubular injury, including 1 case of ischemic tubular insult (probably the result of hypotension), 3 cases of acute pyelonephritis, and 1 patient with tubular nephrocalcinosis. Ten control patients had fundamentally vascular lesions: 7 had nonspecific ischemic nephrosclerosis, 2 had vasculitis (one in a healing phase and the other idiopathic, acute, and necrotizing with associated acute necrotizing glomerular lesions), and 1 had malignant nephrosclerosis. Two of the control cases had allograft rejection, one chronic and the other combined acute and chronic. One control case had end-stage renal disease.

Immunofluorescence

Twelve of the biopsies from the patients with CGN had adequate glomeruli for immunofluorescent study. Seven of these showed varying numbers of capillary wall deposits, generally containing IgG, IgM, and C3 in a segmental to global granular pattern. Three of the biopsies had combined mesangial and capillary wall deposits with IgA, IgM, and C3 components present. Two of the biopsies demonstrated no immunoglobulin or complement deposition. Abundant staining of portions of earlier crescents by anti-human fibrin was seen.

Electron Microscopy

Each biopsy from patients with CGN had from 1 to 9 glomeruli examined by electron microscopy. Three of the biopsies revealed electron-dense deposits confined to the glomerular basement membrane of the capillary wall: in 2 of these, the deposits were subepithelial and intramembranous, and in the third, subendothelial and intramembranous. Two of the cases had mesangial deposits only. Three specimens had combined mesangial and capillary wall deposits. The remaining 6 specimens had no deposits seen in electron-microscopic examination. Two of these latter specimens corresponded to 2 of the specimens shown to be negative by immunofluorescence. Review of the immunofluorescence staining patterns of the remaining 4 specimens shown to be negative by electron microscopy revealed focal or segmental patterns of immunoglobins and/or complement, which would readily explain negative findings by electron microscopy on the basis of sampling differences.

Description and Quantitation of Type IV Nuclear Bodies

Type IV nuclear bodies were identified under the electron microscope by the presence of a spherical aggregate of 20-nm particles surrounded by a microfibrillar cortex (Figures 3 and 4). They were sometimes found in juxtaposition to the nucleolus but were generally located centrally within the nucleus. Type IV nuclear bodies were identified in toluidine-blue-stained epoxy sections under the light microscope by the presence of a spherical structure containing a central dense core with faintly perceptible granularity surrounded by a clear halo (Figure 2). The core stained slightly more intensely than the adjacent nucleoplasm but was always less intensely stained than the nucleolus.

Type IV nuclear bodies were identified in all specimens obtained from patients with CGN. The total number of tubular cross-sections examined ranged from 236 to 913. Two to six nuclear bodies were seen on the representative thick sections of any given patient. This corresponds to a ratio for each patient of 0.33 to 1.10 nuclear bodies per 100 tubular cross-sections examined (Table 2) with a mean ratio of 0.67 ± 0.27.

Six of the 43 controls had Type IV nuclear bodies identified by light microscopy. The number of tubular cross-sections evaluated on the individual control

Table 2—The Frequency of Type IV Nuclear Bodies in Patients With Crescentic GN

Patient	Number of Type IV nuclear bodies	Number of tubule cross-sections examined	Ratio of nuclear bodies per 100 tubular cross-sections
1	2	583	0.34
2	2	236	0.85
3	2	317	0.63
4	6	549	1.10
5	5	936	0.53
6	4	569	0.70
7	3	913	0.33
8	2	556	0.36
9	2	226	0.88
10	3	398	0.75
11	3	279	1.08
12	3	882	0.34
13	2	456	0.44
14	6	593	1.01

Table 3—The Frequency of Type IV Nuclear Bodies in Control Patients Without Crescentic GN

Patient	Number or Type IV nuclear bodies	Number of tubule cross-sections examined	Ratio of nuclear bodies per 100 tubular cross-sections
1	0	499	0
2	0	156	0
3	0	829	0
4	1	372	0.27
5	0	465	0
7	1	509	0.20
8	0	569	0
9	0	461	0
10	1	409	0.24
11	0	344	0
12	1	218	0.46
13	0	523	0
14	0	164	0
15	0	375	0
16	0	279	0
17	0	360	0
18	0	463	0
19	0	140	0
20	0	187	0
21	1	339	0.30
22	0	256	0
23	0	907	0
24	2	947	0.21
25	0	371	0
26	0	241	0
27	3	336	1.19
28	0	419	0
29	0	212	0
30	0	590	0
31	0	104	0
32	0	449	0
33	0	353	0
34	0	820	0
35	2	177	1.13
36	0	306	0
37	0	1805	0
38	0	467	0
39	0	469	0
40	0	394	0
41	0	399	0
42	0	545	0
43	0	507	0

cases was 104 to 1805. The number of Type IV nuclear bodies seen for any given case varied from 0 (on 37 of the controls) to a maximum of 3. This corresponds to a ratio of 0–1.19 nuclear bodies per 100 tubular cross-sections examined (Table 3) with a mean ratio of 0.09 ± 0.26. The difference in mean ratio between the CGN and the control group was determined to be statistically significant ($P < 0.05$).

Electron-microscopic examination by a second independent observer confirmed the presence and frequency of Type IV nuclear bodies determined by thick-section evaluation. Only two additional cases containing Type IV nuclear bodies were detected by electron microscopy. The core of these bodies contained more dispersed granules when compared with the other bodies seen.

The Type IV nuclear bodies were most frequently seen in tubular epithelium at the proximal tubular level (in all 14 of the cases of CGN and in 6 of the controls). Additional sites in which nuclear bodies were observed in the CGN biopsies included an epithelial cell of a collecting duct, a fibroblast, and a cell of a developing crescent. Two of the controls had Type IV nuclear bodies within interstitial fibroblasts. When nuclear bodies were seen in tubular epithelial cells, it was generally in association with ultrastructural evidence of a mild to moderate injury or repair phenomena such as disorder of the brush border (Figure 3), increased numbers of secondary lysosomes, or underlying basement membrane thickening. By contrast, there was no evidence of pathologic cellular alterations in the fibroblasts or in the parietal epithelial cell of the crescent when these contained nuclear bodies. In several of the cases in which nuclear bodies were seen in tubular epithelium by electron microscopy, lymphocytes were observed insinuating between adjacent epithelial cells and between an epithelial cell and the tubular basement membrane.

Simple nuclear bodies were ubiquitous among the renal biopsies examined and were not quantitated. No virus or virus-like structures were observed in any of the 14 cases of CGN nor in any of the 15 control cases examined at the ultrastructural level. In addition, no evidence of a possible viral infection such as disintegration of nucleoli or margination of chromatin was seen. Tubuloreticular inclusions, considered to be a cytoplasmic response to a viral infection,[17] were also

searched for. Two cases of idiopathic CGN had tubuloreticular inclusions identified in glomerular endothelial cells. One control patient with systemic lupus erythematosus displayed these inclusions within glomerular endothelium.

Discussion

Previous studies reporting nuclear bodies in association with renal disease have been sporadic and have been characterized frequently by descriptions of only simple nuclear bodies or heterogeneous groups of nuclear findings. The "light" nuclear bodies described by Collan and Lähdevirta[15] in cases of nephropathia epidemica were noted in conjunction with nuclear vesicles and structures interpreted as possibly representing viral nucleocapsids. The nuclear bodies seen in the biopsy of the hypomagnesemic patient studied by Runeberg et al[14] were recorded as "non-chromatin areas." In 1980, Stachura[18] reported the finding of several types of glomerular and tubular intranuclear inclusions in 22% of cases of CGN. The inclusions were not subclassified; and, in particular, Type IV nuclear bodies were not specifically identified. Representative photographs clearly depicted a variety of structures only some of which fulfilled criteria for simple nuclear bodies. We have observed a number of such structures routinely in renal biopsies representing a variety of disease processes and concur with the hypothesis that these may be markers of cellular damage. We feel it is apparent, however, from our findings that specific quantitation of Type IV nuclear bodies as a distinct subset of nuclear structures was most helpful and allowed us to determine their marked frequency in all cases of CGN examined.

In view of the frequent appearance of nuclear bodies with viral disease, it seems appropriate to consider the possibility that the association that we have observed between CGN and the high frequency of Type IV nuclear bodies in the renal tubular epithelium suggests a viral etiology for rapidly progressive glomerulonephritis (RPGN). Several reports relate occurrences of Goodpasture's syndrome in conjunction with influenza,[19,20] and Wilson and Smith[21] noted serologic evidence of influenza A_2 infection in another patient with Goodpasture's syndrome. The electron-microscopic examination of renal biopsies from an extensive series of 24 patients with CGN failed to reveal virus-like particles.[22] We, similarly, found no viruses or virus-like particles in the 14 CGN cases examined ultrastructurally in our study. However, in support of the possibility of a viral role in the production of CGN even in the absence of recognizable viral structures, it is well known that late effects of viral infection may produce overt disease after the period of virus detection has passed— eg, Coxsackievirus B_3-induced cardiomyopathy of mice.[23] Pertinent, also, to the issue of viral etiology for CGN is our finding of tubuloreticular inclusions within glomerular endothelial cells of biopsies from two patients with idiopathic RPGN. Although it is established that these inclusions are not themselves composed of viral particles, they may be a manifestation of cellular response to viral infection.[17,24] The only control case in our series with such tubuloreticular structures was that of a patient with systemic lupus erythematosus, a disorder known to be associated with these structures.[17]

Of particular relevance to our current study is the report by Margolis et al[25] of experimental reovirus encephalitis in suckling rats, in which Type IV nuclear body formation was observed as a "satellite" phenomenon occurring *adjacent* to areas of maximum virus injury. In this model, cytoplasmic viral inclusions (indicative of the presence of virus) and nuclear bodies were never seen in the same cell. Furthermore, while cytoplasmic reovirus inclusions first appeared at 2–3 days, were conspicious from 4 to 8 days, and were absent after 10 days, nuclear bodies were prominent at 7–25 days and seen as late as 72 days. Finally, although inoculation of infected tissues into rats produced both typical reovirus cytoplasmic inclusions and nuclear bodies, similar inoculation into rat embryo cell cultures produced characteristic cytoplasmic inclusions but no nuclear bodies. These observations suggested several possibilities to the authors: first, that complex nuclear bodies may be a manifestation of "submorphologically evident" viral infection with viral alteration of the host nuclear or nucleolar composition; second, that the formation of complex nuclear bodies may be a phenomenon of interferon production; third, that cells infected by virus may release into the adjacent milieu a chemical mediator which may activate a nuclear reaction in adjacent cells morphologically displayed as complex nuclear bodies. Each of these possibilities would seem equally valid in the explanation of the frequent appearance of Type IV nuclear bodies in CGN. It may be that the time frame of the disease is such that the biopsy specimen is obtained after the period in which virus particles are most likely to be present, but nuclear bodies persist as a later morphologic marker of virus effect.

If viruses are indeed the etiologic agents of CGN, what factor or factors account for the production of such a large number of crescents, the hallmark of RPGN? In an experimental rat model it was shown that CGN could be produced simply by the intraperitoneal injection of interferon, a naturally occurring

antiviral agent.[26] In human CGN, it is conceivable that the presence of viruses elsewhere in the renal tissue induces nuclear body formation and the interferon produced by the infected cells induces crescent formation.

It is pertinent to such a hypothesis for us to examine those cases in which nuclear bodies were seen in the absence of CGN, to determine whether these patients may also have an underlying viral illness. Two of the patients had systematic lupus erythematosus, a disorder associated with elevated titers to a variety of viruses.[27,28] Another was a 7-year-old boy with mesangial proliferative GN, which developed acutely in association with fever, pneumonitis, a nonstreptococcal upper respiratory tract infection, and lymphadenopathy. All of these symptoms spontaneously resolved over the next month and strongly suggested a self-limited viral infection. A very similar control case was that of a 25-year-old man with acute onset of fever, fatigue, malaise, arthralgia, and a skin rash interpreted by a dermatologist as being a viral exanthem, who on admission had mild elevation of serum bilirubin and SGOT and leukocytosis. All of these clinical and laboratory findings cleared completely within 3 weeks without therapy, strongly suggestive of an acute viral illness. The patient whose renal morphologic lesion was diabetic glomerulosclerosis came to renal biopsy because of a work-up of an acute illness characterized by hepatosplenomegaly and fever of undetermined etiology. Another patient had fever, anorexia, and generalized malaise preceding the development of an acute necrotizing vasculitis and acute glomerulonephritis without evidence of immune complex deposition by immunofluoresence or electron microscopy. All 6 of these patients had clinical presentations or coexisting states, which suggested to varying degrees the possibility of a viral component to their illness. Only 2 of this group of 8 cases lacked clinical features particularly suggestive of a potential viral process: one of these was a case of granulomatous interstitial nephritis with a clinical history of sarcoidosis and the other a case of "allergic" interstitial nephritis with a presentation of renal insufficiency and mental confusion but no other information regarding constitutional symptoms.

Another important question which must be addressed is whether the Type IV nuclear bodies merely represent a cellular manifestation of injury and/or repair. While there is no way that such an argument could be conclusively rejected, the absence of complex nuclear bodies in those control cases in which significant tubular injury was produced by pyelonephritis, active tubulointerstitial nephritis, malignant nephrosclerosis, and renal allograft rejection would suggest that response to injury or regenerative phenomena alone is not responsible for the formation of nuclear inclusions.

Finally, the finding of Type IV nuclear bodies might represent the presence of virus, either preceding or accompanying the acute onset of renal insufficiency, without the virus necessarily being the sole etiologic agent in the formation of CGN. Nevertheless, the possibility of a viral agent contributing to the development of CGN must be carefully considered.

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