INTRAENDOTHELIAL INCLUSIONS IN SYSTEMIC LUPUS ERYTHEMATOSUS

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An electron-microscopic investigation was made of biopsy material from the kidneys of 10 patients with systemic lupus erythematosus with kidney involvement. In 6 cases virus-like inclusions, formed of filaments from 290 to 800 Å in length and up to 200 Å in width, were found in the endothelial cells of the glomerular capillaries. No such inclusions were found in renal biopsy material from 20 patients with ordinary chronic glomerulonephritis.

The possibility of the viral etiology of systemic lupus erythematosus (SLE) is at present being debated vigorously. The virus theory could explain changes in the antigenic structure of the nuclear components of the cell and the formation of a virus DNA–protein complex.

Investigations into the virus etiology of SLE were spasmodic until the end of the 1960s. In 1966, Mellors and Huang [13] found virus-like inclusions during electron-microscopic investigation of the kidneys of NZB/NZW mice with a lupoid syndrome. In 1968, Fresco [4] found numerous tubular structures in the kidney tissues of a 54-year-old woman with lupus nephritis inside electron-dense deposits in the basement membrane of the glomerular filter. A little later tubular structures were found inside the glomerular endothelial cells of a patient with acute lupus by Györkey et al. [7]. In the next 4 years similar papers were published in which structures up to 200-280 Å in diameter were described in the endothelial cells of the capillaries [2, 5, 15], the peritubular capillaries [14], and in the tubular epithelium [10] of patients with lupus nephritis and also in kidney tissue cultures from patients dying from SLE [8].

The investigation described below was carried out to obtain further evidence in this direction.

EXPERIMENTAL METHOD

Biopsy specimens from the kidney from 10 patients with SLE (9 women and 1 man aged 16-47 years) were investigated. The duration of the disease varied from 1 to 5 years and the clinical picture in 9 of 10 patients was dominated by lesions of the kidneys. Four patients had lupus nephritis with a nephrotic syndrome, 5 patients had nephritis without a nephrotic syndrome, and 1 patient had no clinical manifestations of kidney damage. Histologically the kidney lesions in 3 patients were diagnosed as lupus nephritis, in 7 patients as nephritis without any characteristic histological features of SLE (membranous, membrano-proliferative, or fibroplastic).

The control group consisted of biopsy material from the kidneys of 20 patients with chronic glomerulonephritis (11 men and 9 women), 5 of whom had a nephrotic syndrome.

On histological investigation of kidney biopsy specimens from 5 patients membranous glomerulonephritis was found, proliferative in 2 patients, membrano-proliferative in 10, and fibroplastic in 3 patients.

The material for electron-microscopic investigation was fixed in 1% buffered osmium tetroxide solution, dehydrated in alcohols of increasing concentration, and embedded in Araldite. Sections were cut on the LKB ultratome and examined in the UÉMV-100K electron microscope.

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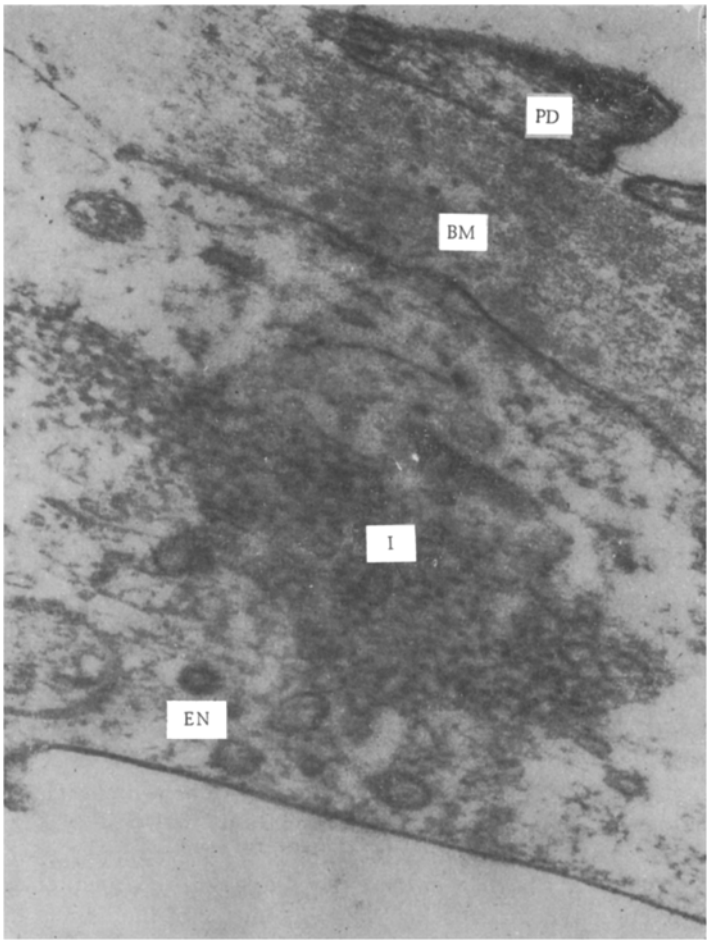

Fig. 1. Glomerular filter of a kidney in SLE: inclusions (I) consisting of reticular structures can be seen in the endothelium (EN); BM) basement membrane; PD) small process of a podocyte (45,000×).

EXPERIMENTAL RESULTS

In 6 of 10 cases virus-like inclusions formed by filaments from 290-890 Å in length and up to 200 Å in width, were found in the epithelial cells of the glomeruli of patients with SLE. The filaments were composed of tubules or chains of osmiophilic granules and they formed reticular structures. The inclusion were located in the peripheral part of the cytoplasm and in some cases they were connected with dilated cisterns of the smooth endoplasmic reticulum (Fig. 1); no inclusions were present in the mesangial cells of the glomerular and tubular epithelium.

The inclusions thus revealed were similar to those described in the literature. They were similar to myxoviruses or paramyxoviruses in tissue culture. According to Norton [14], the inclusions in SLE are similar to nucleoprotein bands isolated from myxoviruses or paramyxoviruses. Kawano et al. [12] found a ribonucleoprotein characteristic of RNA-containing viruses in the inclusions; similarity between the inclusions and RNA-containing viruses is also indicated by the fact that they are destroyed more readily by ribonuclease than by deoxyribonuclease.

Meanwhile there were morphological differences between the inclusions of SLE and viruses: the SLE inclusions were much larger than those associated with myxovirus infection. The diameter of the tubules of the known myxoviruses is 90-180 Å whereas the diameter of the tubular inclusions in SLE varies from 200 to 310 Å). The inclusions in SLE are often connected with the endoplasmic reticulum, a feature uncharacteristic of viruses. Evidence against the virus hypothesis is given by the failure to isolate viruses from the kidney tissue of patients with SLE with inclusions in the endothelium [3, 15]. Some workers accordingly consider that the inclusions are a product of the cell response to injury [9, 16], deformed component parts of the cell [15], or a manifestation of phagocytosis of nuclear material by the cells [10, 11]. The possibility cannot be ruled out that they are a system of microtubules of the cell visible during functional stress.

Regardless of the nature of the inclusions they are sufficiently characteristic of SLE and they correlate with the degree of its activity. For instance, inclusions were found in all four patients with a lupus nephrotic syndrome and in 2 of the 5 patients with active lupus nephritis but they were not found in patients with clinically healthy kidneys. Correlation also was found with the histological type of nephritis: inclusions were found in all 3 patients with lupus nephritis but in only 3 of 7 patients with nephritis and with no characteristic histological features of SLE. Marked immunofluorescence of γ-globulin was found in all patients with inclusions in the kidney tissue. No connection could be found between the inclusions and previous treatment with corticosteroids and cytostatics.

That the virus-like inclusions play a definite role in the development of systemic lupus is confirmed by the high specificity of these findings for SLE. In a retrospective assessment of 260 electron micrographs of the kidneys, Kawano et al. [12] found analogous structures in 28 cases: in 25 patients with SLE, in 2 patients with incompletely confirmed SLE, but only in 1 patient with chronic glomerulonephritis. Bloodworth and Shelp [2] observed tubular inclusions in 62% of kidney biopsy specimens in SLE but only in 2.4% of kidney biopsy specimens from patients with other diseases; Grausz et al. [6] observed them in 29 of 30 patients with SLE but in only 1 of 38 patients with other diseases, and Tisher et al. [16] observed them in 30 of 34 kidney biopsy specimens from patients with lupus nephritis and in only 8 of 190 biopsy specimens from patients with other nephropathies. The present writers found no inclusions in kidney biopsy material from any of 20 patients with glomerulonephritis.

The diagnostic value of these inclusions is confirmed by the observations of Grausz et al. [6], who found tubular structures in the intact (clinically and histologically) kidneys of 2 patients with lupus discoides (a few years later both developed the typical picture of SLE with nephritis). In one case described by Garancis [5] multiple inclusions were found during biopsy of the kidney of a patient with a diagnosis of dermatitis herpetiformis with proteinurea, but later the diagnosis of SLE was confirmed. Admittedly in a recent communication, Bariéty et al. [1] were more hesitant regarding the specificity of the inclusions for SLE. These workers investigated 376 biopsy specimens of the kidneys (material from several Paris hospitals) and found inclusions in 89% of specimens from patients with SLE and in 24.5% from patients with other nephropathies. The discovery of virus-like inclusions in 73% of biopsy specimens from kidneys transplanted more than 1 year previously whereas in the early stages after transplantation inclusions were found in only 7 of 40 biopsies is particularly interesting. The discovery of inclusions in transplanted kidneys raises the question of the role of ischemia in the genesis of the inclusions in contradistinction to the virological hypothesis, although there are no grounds for considering that the inclusions in SLE and in transplanted kidneys are identical, despite their ultrastructural similarity.

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