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STORAGE FUNCTION OF THE GLOMERULAR EPITHELIUM AND THE RELATION OF NEPHRITIS AND NEPHROSIS

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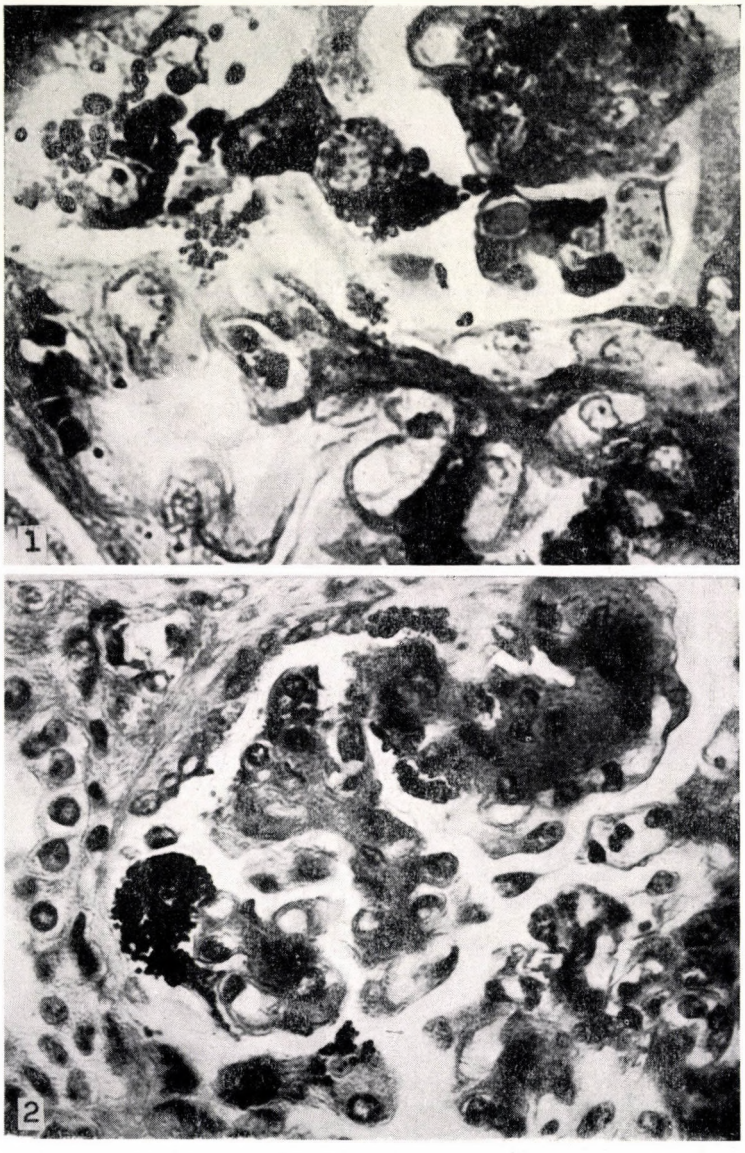
In the literature dealing with kidney disease there are few data concerning the behaviour and role of the epithelium of the glomerular tufts. This is partly due to the fact that the changes are so delicate that their registration *post mortem* is hardly feasible, and partly to the lack of a proper technique for demonstrating them. Our material originating from kidney biopsy and some autopsies showed, however, certain changes, by virtue of which it has been felt necessary to revise the notion that the role of the glomerular epithelium is but a passive one. Although a less marked form of the changes to be described has been sporadically noted the following report will discuss only the typical and demonstrable cases.

I

The first case was that of a female subject 42 years old whose blood pressure had been above normal for several years. Hypertensive complaints had, however, begun only six months before death occurred. Prior to death she had been treated for two months at the 3rd Department of Medicine of Budapest University. Blood pressure was fixed at 240/130 mm mercury. There were haemorrhages at the ocular fundi and papillary and retinal oedema. Specific gravity of the urine was about 1010 Esbach 0,18 per 100 ml. The sediment contained 5—6 erythrocytes, and 1—2 leucocytes. NPN was 27 : C_K 60 ml. Urologic examinations and the high Addis count suggested chronic pyelonephritis along with malignant hypertension. The patient was therefore transferred to the 3rd Department of Surgery, where thoraco-lumbar sympathectomy, decapsulation and kidney biopsy were performed. The patient was unwell following the operation, her blood pressure decreased to 96/60 mm mercury, she fell into a deep coma followed by symptoms of brain enbolism, and on the sixth day after the operation she died.

Necropsy disclosed cardiac hypertrophy, pulmonary oedema, confluent bronchopneumonia, and multiple fresh emollitions in the brain. The kidneys were comparatively small, compact, their surface was finely granulated.

Histology revealed specific hypertensive changes but no arteriolar necrosis in the blood vessels. In the kidneys where signs of chronic nephritis, some scarred and many roughly lobated glomeruli were found with tufts showing hyaline degeneration and with proliferation of the epithelium of the glomerular tufts. The biopsy material from the kidney was stained with our own trichrome dye, a combination of Heidenhain's Azan and Mallory's phosphotungstic acid haematoxylin, for the simultaneous demonstration of the various kinds of hyalin and of the so-called fibrinoid substance [9]. By this staining method it was revealed that the cytoplasm of the proliferating glomerular epithelium frequently contained large numbers of comparatively small or large granules staining a dark violet, a reaction characteristic of fibrinoid substances ; such granules would, at times, fill the entire cell (Figs. 1 and 2). It was further revealed that the epithelial cells of some proximal tubules also contained granules staining in a similar manner. Lipoid staining revealed fine fat granules in the epithelium of the proximal tubules whereas none



Figs. 1 and *2*. Part of glomerulus from case No. 1. Enlarged epithelial cells of the glomerular tufts filled with granulae staining as fibrinoid. (Combined trichrome dye, 600×)

were found in the glomeruli. The fibrinoid granules seen in the glomerular epithelium were no longer demonstrable *post mortem*. (Naturally, the term «fibrinoid» refers here merely to be stainibility of the substance ; it does not, however, follow that chemically it can be identified with common fibrin or with a substance produced during fibrinoid degeneration.)

In another case, a male infant 4 moths of age had been taken ill with bronchopneumonia, in the course of which oedema and albuminuria had developed. The condition had gradually improved, the oedema had disappeared. A few weeks later he had had another attack of pneumonia accompanied by severe oedema, albu min $+++$ and a few hyaline casts in the urine. He was once more admitted to hospital with pneumonia and suspected nephrosis. The condition deteriorated and a week later, at the age of 6 months, the patient died. Before death, NPN amounted to 46 mg per 100 ml. serum albumin to 2, globulin to 2,2 g per 100 ml.

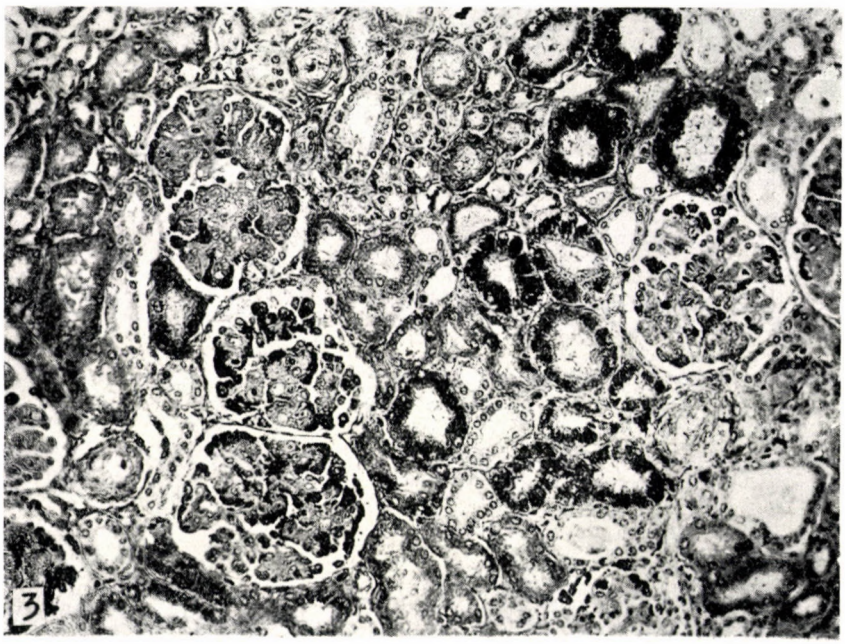


Fig. 3. Section from the kidney of case No. 2. Dark staining epithelial cells of the glomerular tufts full of granulae on the periphery of the glomeruli. The epithelium of the proximal tubules is in part also filled with similar granules. (Combined trichrome dye, 100×)

At necropsy, bilateral bronchopneumonia, anaemia, severe oedema and rachitis were found. On the cut surface of the kidneys the widened renal cortex was of a pale yellowish hue.

Histology showed anaemic glomerular tufts, covered with proliferating epithelium, the cytoplasm of which was to a great extent filled with fibrinoid granules (Figs. 3. and 4). Large quantities of similar granules were found in the epithelial cells of some groups of proximal tubuli. Lipoid stain revealed many fine fat droplets in the proliferating epithelial cells of the tufts, but none could be demonstrated in those of the tubules. Singularly, in a number of vascular lumina the congealed plasma took on lipoid stain, indicative of lipaemia.

II

In connection with Szentiványi and Székely's investigations into the problem of Masugi nephritis, conducted at the 3rd Department of Medicine of Budapest Medical University, we had occasion to examine the problem experimentally. Acute glomerulonephritis, characterized by proliferating glomerular epithelium, was found in rats inoculated intravenously with nephrotoxic

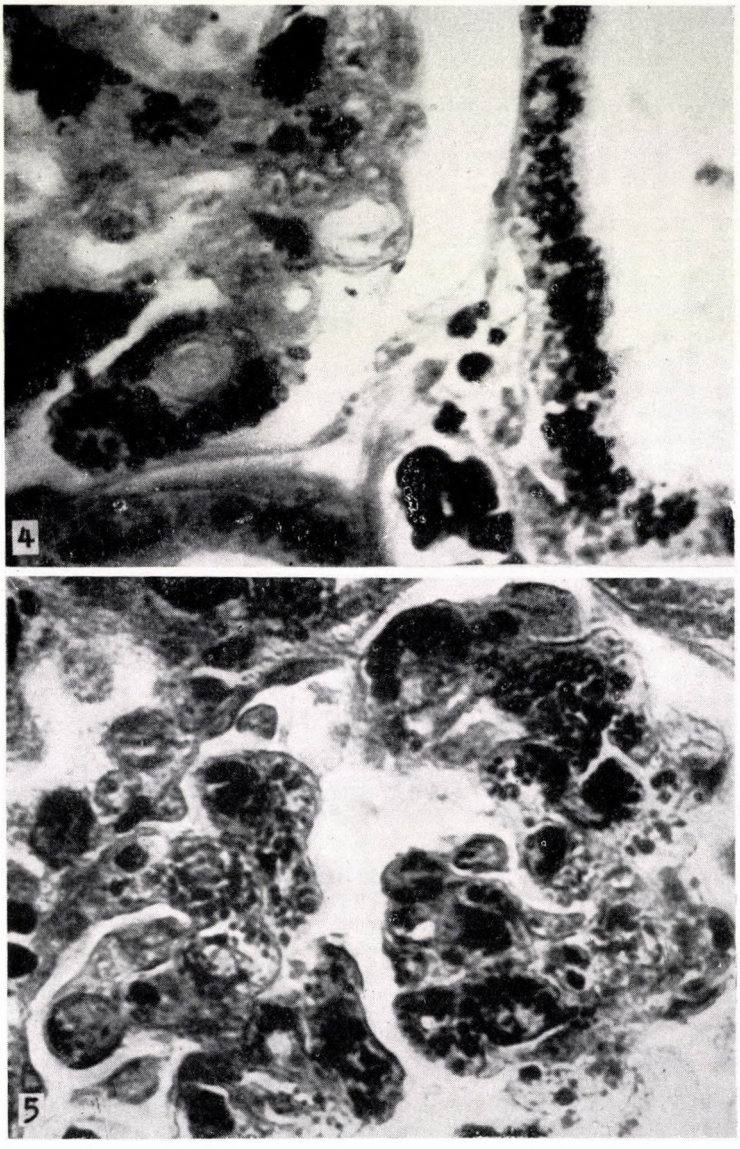


Fig. 4. Epithelial cells packed with granulae staining as fibrinoid on the periphery of the glomerular tufts. The adjoining proximal tubular epithelial cells show similar granulation. (Case No. 2. Combined trichrome dye, 600×)

Fig. 5. Specific nephrotoxic nephritis, rat No. II/6, showing similar type of granulation in the epithelium of the glomerular tufts. (Combined trichrome dye, 600×)

rabbit serum and killed 10 days after the inoculation. The epithelial cytoplasm of the glomerular tufts contained a large number of fine granules staining as fibrinoid, and similar granules were found also in the tubular epithelial cells though in considerably lesser number. (Fig. 5.) The granules in the epithelium of the glomerular tufts stained intensely with Sudan, but in the tubular epithelium no lipoid granules were discernible. In some places, the plasma congealed in the blood vessels also stained with the lipoid dye. Attempts at demonstrating in frozen sections the granules showing in embedded preparations fibrinoid staining properties, have failed. However, when the frozen sections had been pre-treated with some lipoid solvent, the fibrinoid granules took on the stain. According to this, the granules accumulating in the epithelial cells of the glomerular tufts consist of a mixture of lipoid and protein, the protein component of which is stainable only after the lipoids have been dissolved. The granulation in the epithelium of the glomerular tufts showed a similar behaviour in the case of the infant reported above. It should, however, be mentioned that in another series of nephrotoxic nephritis cases, the epithelium of the glomerular tufts was only slightly granulated, while the thickening of the basal membrane and its fibrinoid degeneration were more marked. This was accompanied by extreme accumulation of protein droplets in the tubular epithelium. There is apparently a certain interrelation between the storage function of the epithelium of the glomerular tufts and of the tubular epithelium.

Discussion

The findings reported above raise two problems. First, the behaviour of the epithelium of the glomerular tufts ; second, the interrelation of glomerulonephritis and of lipoid nephrosis. Our obsevations proved beyond doubt that the epithelial layer enveloping the glomerular tufts is capable of storing protein and lipoid. Beside foreign authors, the Hungarian researchers *Jancsó* and *Gábor* observed storage of protein droplets in the tubular epithelium after administrating of protein stained with Germanin (16, 19, 22). Our own observations indicate that the protein may previously accumulate in the epithelium of the glomerular tufts, where it undergoes some chemical change. It should be mentioned that in other cases of chronic nephritis accumulation of materials derived perhaps from the decaying basal membrane were also observed.

It was demonstrated by several authors, using antigen labelled with radioactive elements or fluorescent materials, that in nephrotoxic nephritis the antigen-antibody reaction occurs in the glomeruli. Using fluorescent antigen *Hill* and *Cruickshank* found that beside the basal membrane, the epithelium of the glomerular tufts was also brightly fluorescent (7, 11). This led us to assume, that the protein granulation was a result of the antigen-antibody conjugation appearing in allergic glomerulonephritis. This would agree with *Jancsó*'s experiments demonstrating in the Arthus reaction the accumulation of the antigen-antibody complex in the histiocytes of the skin, by using antigen tagged with Germanin (13). It seems, however, more probable that in our cases it was the superfluous, unfixed antibody that accumulated in the epithelium of the glomerular tufts.

Concerning the relation of nephritis and nephrosis, most authors are of the opinion that lipoid nephrosis is no specific disease but merely a variety of glomerulonephritis. (2. 4. 5. 17.) Almost without any exception, nephrosis in adults goes over into chronic nephritis, and the so-called genuine nephrosis occurs only in infancy. Others again consider lipoid nephrosis as a specific kind

of disease [6]. *Ehrich* et al. maintain that glomerulonephritis and lipoid nephrosis are related merely aetiologically, nephritis being characterized by productive inflammation, while nephrosis by fibrinoid degeneration of the basal membrane, in other words by a regressive change. [8]. In contrast with this, our own observations invite attention to the morbid change in the epithelium of the glomerular tufts. According to *Moeller*, it depends on the condition of the reticuloendothelial system whether or not it is able to produce biologically more valuable globulins, antibodies and hypertensinogen, thus creating the hypertensive form of reaction [15]. If the reticuloendothelial system is functioning unsatisfactorily, the globulins produced are inferior in value. This might be the cause of the high level of alpha und beta globulins typical of nephrosis, dyspoteinaemia, which manifests itself clinically and morphologically in the nephrotic syndrome. According to the above, nephrosis and nephritis are but two different types of reaction to the same kind of lesion, and it is the age and the reactivity of the organism which will decide whether the subject will develop nephrosis that is apt to heal, or whether his condition will lead into gravely progressive nephritis.

The fact, that both in infantile nephrosis and in the *Masugi* nephritis of rats, an increase of plasma lipoids was observed in the lumen of renal blood vessels, along with the accumulation of abnormal protein-lipoid complexes in the epithelium of the glomerular tufts, indicates that the changes in the protein and lipoid composition of the blood plasma are independent from the kidneys. It should be mentioned, that, according to certain data, lipoids act as inhibitors in allergic processes, inhibiting the antigen-antibody fixation (10, 18).

Considering the morphologic similarities in the above cases, the question arises whether the diseases under examination are not essentially identical, differing rather in the variance of the pathomechnism. Such variance may among others be due to the fact that in cases whose reactivity is vigorous, the allergic process manifests itself with a primary renal inflammation, while in the nephrotic patient with low reactivity the primary effect consists in a change of the plasma albumin, with the renal disease as a consequence. We consider the granulae in the epithelium of the glomerular tufts as a consequential change, the meaning of which in the subsequent development of the morbid process is not yet clear. Owing to the rarity of the changes, we do not wish to draw far-reaching conclusions from the observations. The development of the changes might possibly depend on special biochemical conditions, which require further studies.

We wish to state in conclusion that the comments made last were meant to refer only to the so-called lipoid nephrosis. The term «nephrosis» as used in pathology, however, is considered not dispensable for designating certain primary degenerative tubular changes — especially, those of toxic-infectious origin —, as has been pointed out by *Abrikosov*, *Anderson*, *Boyd*, and *Korpássy* [1, 3, 5, 14].

Summary

In cases of lobular-membraneous glomerulonephritis, infantile nephrosis and nephrotoxic nephritis in rats, granular accumulation of protein and lipoid was observed in the epithelial lining of the glomerular tufts. The granulae gave a positive fibrin staining. A similar granulation was observed in the epithelium of the proximal tubules. In part of the cases there was a simultaneous increase of plasma lipoids. In connection with the storing function of the glomerular epithelium, the relation between nephrosis and nephritis has been discussed.

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НАКОПИТЕЛЬНАЯ ФУНКЦИЯ ЭПИТЕЛИЯ КЛУБОЧКИ И ВОПРОСЫ ВЗАИМООТНОШЕНИЯ МЕЖДУ НЕФРИТОМ И НЕФРОЗОМ

П. ЭНДЕШ и Л. ТАКАЧ-НАДЬ

Авторы наблюдали в случаях хронического лобулярно-перепончатого гломерулонефрита, нефроза в грудном возрасте, далее у крыс в случае нефро-токсического нефрита зернистое накопление белковых липоидов в эпителии петель клубочек. Зернышки показали положительную окраску на фибрин. Подобная зернистость наблюдалась также и в эпителии проксимальных канальцев. В одной части вышеприведенных случаев авторы наблюдали одновременно размножение плазменных липоидов. В связи с этой функцией накопления эпителия петель авторы занимались также и вопросами взаимоотношения между нефрозом и нефритом.

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