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DIABETIC ANGIOPATHY AND GLOMERULOSCLEROSIS

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Introduction

It is well known that diabetes mellitus leads to early and grave arteriosclerosis. Since the introduction of insulin therapy diabetic arteriosclerosis has gained a particular practical importance. *Joslin*'s data [17] show that in the last 50 years the rate of diabetics dying in coma has decreased from 63,8 per cent to 1,9 per cent, while during the same period the number of deaths caused by vascular lesions has risen from 17,5 per cent to 69,2 per cent. Arteriosclerosis has thus become the most important problem of diabetes since the introduction of insulin. In Hungary, it was *Hetényi* [14, 15] who on the basis of statistical data has emphasized the significance of diabetic vascular lesions.

Diabetes affects the coronary arteries and those of the extremities in the first line. Still, large arteries also suffer, either in the form of atheromatosis or calcification, while in small arteries, arterioles and capillaries hyaline arteriosclerosis appears. Since in non-diabetic arteriosclerosis the changes in the arterioles and capillaries are never so marked as those found in diabetics, advanced hyalinosis of the small arteries is held by some authors to be almost characteristic of diabetes.

This is the reason why, notwithstanding the absence of special anatomical and histological changes, the term diabetic angiopathy is currently employed in clinical medicine. The clinical manifestation of this type of angiopathy consists, beside diabetic retinopathy, in intercapillary glomerulosclerosis, the so-called Kimmelstiel—Wilson's syndrome.

In 1936, *Kimmelstiel* and *Wilson* [19] reported eight cases in which characteristic clinical symptoms had developed in consequence of a hyaline degeneration of the glomeruli. According to them, the hyaline appearing in the intercapillary connective tissue of the glomeruli would extend from the afferent arteriole to the interglomerular connective tissue. *Bell* [4] has distinguished between a nodular and a diffuse type of glomerulosclerosis. The nodular type, characterized by round hyaline globules, has been considered characteristic of diabetes. In the diffuse type, hyaline connective tissue is

uniformly accumulated between the glomerular capillaries, leading to a thickening of the capillary walls.

As established by *Kimmelstiel* and *Wilson*, glomerulosclerosis manifests itself clinically in albuminuria and oedema. In the advanced stage of the disease, the patients develop hypertension, death being caused by renal insufficiency and uraemia in consequence of obliteration of the glomeruli; according to the literature, in 60 per cent of the cases death occurs about 2 years after oedema and albuminuria had first appeared.

Own Investigations

The relationship between diabetes and arteriosclerosis has been studied in this Institute for a long time. Since 1949, 50 cases of diabetes have been worked up, studying the anatomical and histological appearance of the kidneys, as also the lesions of the vascular system. Intercapillary glomerulosclerosis was recorded in 12 of the 50 cases [2].

All diabetics suffering from the Kimmelstiel—Wilson syndrome were of advanced age, the youngest 32, the oldest 75 years old, with an average of 58 years. 8 were females, 4 males (Table I).

TABLE I

No.	Autopsy protocol	Age	Sex	Duration of diabetes	Albumin in urine	NPN mg%	BP	Glomerulosclerosis	Small arteries of organs
1	351/949	57	♀	?	?	?	?	hyaline	hyaline
2	164/950	70	♀	2 years	++++	84	185/80	hyaline	hyaline
3	113/951	62	♂	23 years	++++	84	215/95	grave necrosis	transitory
4	167/951	50	♀	15 years	neg.	36	170/70	hyaline	hyaline
5	310/951	62	♀	11 years	+	?	180/90	hyaline	hyaline
6	440/951	58	♀	14 years	++++	48	190/105	transitory	extensive necrosis
7	553/951	49	♂	17 years	+	?	140/90	transitory	transitory
8	1026/951 John's Hospital	63	♀	11 years	++	?	?	hyaline	hyaline
9	50/952 John's Hospital	54	♂	?	++++	?	130/70	hyaline	hyaline
10	260/952	75	♂	25 years	++++	48	220/90	transitory	extensive necrosis
11	430/952	58	♀	7 years	++++	87	210/100	grave necrosis	extensive necrosis
12	50/953	32	♀	20 years	++++	153	175/110	grave necrosis	transitory

Although the clinical symptoms of the Kimmelstiel—Wilson syndrome had varied in seriousness from patient to patient, a very marked albuminuria or an increase in the blood pressure had occurred in every one of them. In 3 instances, the condition had been diagnosed during life (cases Nos. 6., 10., and 11.), while, in the remaining 9 cases, the diagnosis had been either hypertension (increased blood pressure having been the chief symptom) or chronic nephritis (in cases of grave albuminuria associated with haematuria and azotaemia).

The findings of our anatomical and histological studies will be reported in two groups, the first dealing with the renal lesions, the second with those of the small arteries.

Renal Lesions

The presence of the Kimmelstiel—Wilson syndrome may be suspected at gross examination already. The incipient phase of the disease is marked by an increase in size of the kidneys ; their surface is greyish-yellow, with a clear-cut borderline between cortex and medulla. In the later stage granules of the size of a pinhead or a millet seed develop on the renal surface ; they arise in the same way as in chronic nephritis. The granules have a peculiar yellowish colour, owing to infiltration of the tubules with lipoid. Lentil-sized retractions, owing to the cicatrization of nephrons destroyed by glomerulosclerosis, may be observed between the granules.

Although the macroscopical picture may already suggest the presence of glomerulosclerosis, the Kimmelstiel—Wilson syndrome cannot be diagnosed with certainty without histological examination. In every one of our cases glomerulosclerosis of either the focal or the diffuse type could be observed. The histological changes were similar to those reported in the literature. In our opinion, however, the histogenesis of glomerulosclerosis differs in most cases from the one accepted in the literature and described in the introduction.

Studying the histogenesis of intercapillary glomerulosclerosis, it was found that the glomerular lesion begins with capillary changes manifesting themselves in an increased permeability of the capillary wall. This leads to an albuminous imbibition of the mesoangium, while, in more serious cases, necrosis of the capillary wall ensues. The capillary loops stain greenish-yellow with van Gieson's stain and bright red with Mallory's trichromic dye, and give a positive McManus—Hotchkiss reaction *(Figure 1)*. The fibrinoid necrosis of the loops is indicated by Weigert's fibrin stain. Lipoids may also be deposited at the site of the necrosis where, in a later phase, a hyaline material appears, staining yellow or red with van Gieson's, and blue with Mallory's method.

Several authors had thought that the substance appearing in the glomeruli was amyloid. On the basis of staining with Congo red, *Fahr*, too, had considered the substance appearing in the glomerulus to be amyloid ; later, however,

he found that Congo red is not specific for amyloid since other proteins may also stain with it. The lesions show no metachromasia on staining with gentian violet, so that the absence of an amyloid reaction helps to distinguish between glomerulosclerosis and amyloid degeneration of the glomeruli. According to our findings, the hyaline degeneration of the glomeruli associates itself with a fibrinoid necrosis developing at the acute stage. Just as fibrinoid necrosis never appears at the same time in all glomeruli, so hyaline degeneration develops likewise in separate foci. It occurs frequently that in some of the glomeruli hyaline nodules are found while other glomerular loops display fibrinoid necrosis. As indicated by Weigert's fibrin stain, the condition begins with fibrinoid necrosis and this is which then becomes hyalinized. The necrotic loops stain blue, while necrotic areas, once hyalinized, do not stain any longer *(Figure 2)*.

Since hyaline degeneration of the glomeruli in the Kimmelstiel—Wilson syndrome is preceded by fibrinoid necrosis of the capillary loops, it seemed obvious that the hyalinosis of the small arteries would show a similar development. Special attention was paid to that circumstance when investigating arterial lesions.

Hyalinosis of Small Arteries

Lesions occurring in the small arteries, arterioles and capillaries of the internal organs have been studied. Two characteristic changes could be recorded in the small arteries, viz. fibrinoid necrosis and hyalinosis.

Fibrinoid necrosis of the arterial, arteriolar and capillary walls was observable in 6 instances. The change was widespread in 3 cases in which the small arteries of nearly all internal organs were found to be necrotized ; diffuse vascular necrosis could be found in the pancreas *(Figure 3)*, spleen, adrenals, liver, kidney and prostate in case No. 6 ; in the pancreas and kidney in case No. 10 ; in the pancreas, kidney, spleen *(Figure 4)*, liver, adrenals *(Figure 5)* and hypophysis in case No. 11. Fibrinoid necrosis of the vascular wall was specially pronounced in capillaries and arterioles, but it was present also in small arteries. While in the arteriolar and capillary walls the necrosis was of the diffuse type, the lesion of the arterial walls was more of a nodular character. Fibrinoid necrosis in the arterioles and capillaries begins under the endothelium with accumulation of a homogeneous substance. The walls become subsequently infiltrated in their whole thickness with the substance. This results in a considerable thickening of the walls, and in narrowing or complete occlusion of the lumen *(Figure 6)*. In small arteries, the process may start in the media leaving the intima intact.

In three further cases (*(Nos. 3, 7 and 12)*, fibrinoid necrosis occurred only in some of the small arteries or arterioles of a few organs (spleen, pancreas, kidney). In these cases in small arteries lesions of »transitory type« were observed; the homogeneous substance in their walls stained very weakly with the fibrin

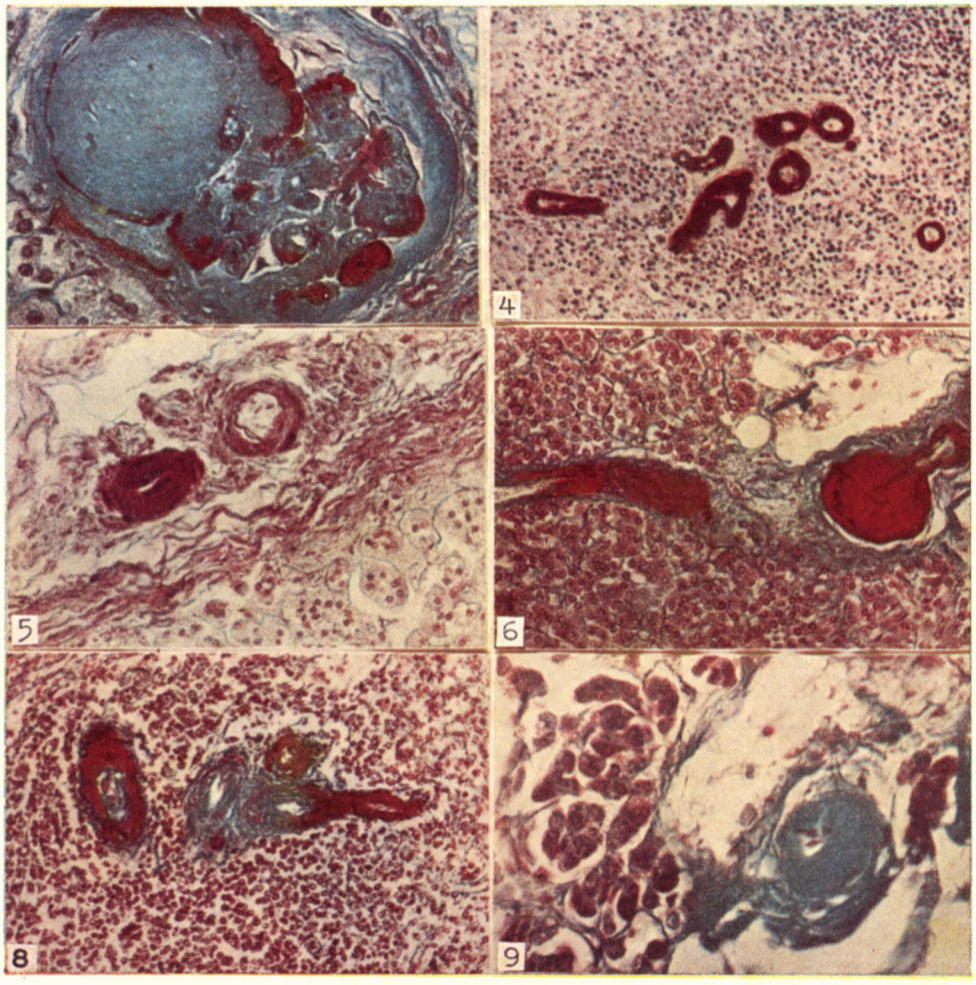

Fig. 1. Fibrinoid necrosis of glomerular capillary loops. Hyaline thickening of Bowman's capsule Necrotic areas red, hyaline areas blue. Mallory's stain

Fig. 4. Fibrinoid necrosis in splenic arteries. Weigert's fibrin stain

Fig. 5. Necrotized wall of one of the arteries of the adrenal gland. Next to it, a comparatively intact small artery. Weigert's fibrin stain

Fig. 6. Fibrinoid necrosis of pancreatic arterioles. Mallory's stain. Extensive thickening of arteriolar wall; obliterated lumen shown in red

Fig. 8. Transition from fibrinoid necrosis to hyalinosis in splenic arteries. Mallory's stain. Necrotic areas red, hyaline areas blue

Fig. 9. Hyaline arteriole with thickened wall and extremely narrow lumen in pancreas, stained blue with Mallory's dye

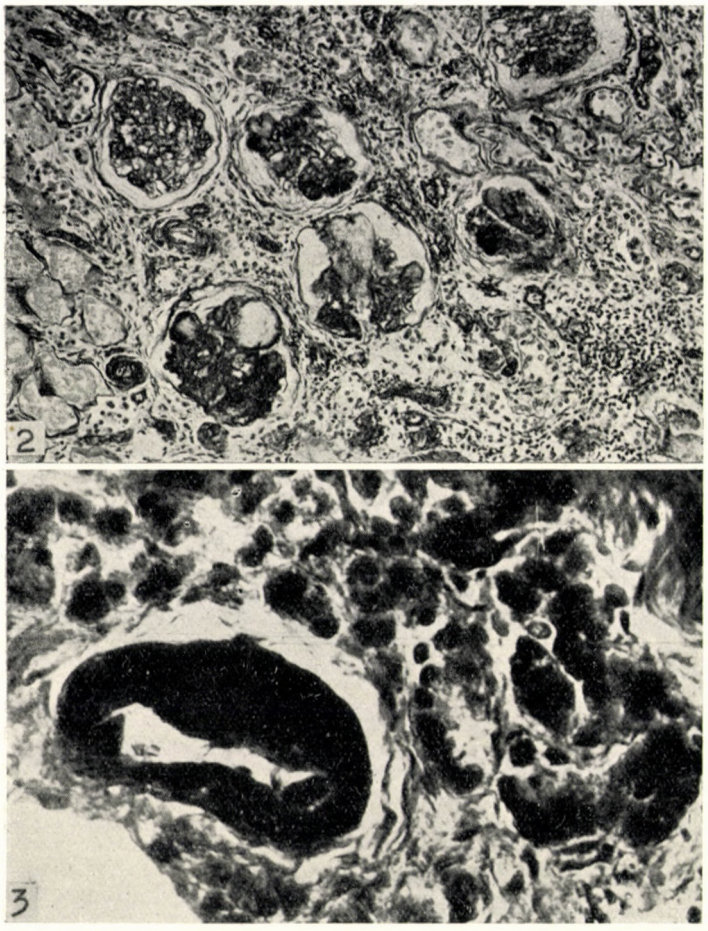

Fig. 2. Necrotic glomerular loops stain intensively with Weigert's fibrin stain; hyalinized Kimmelstiel-Wilson bodies do not stain
Fig. 3. Necrotic small artery in pancreas. Mallory's stain

stain, while indistinct, pale-red clouds appeared on a blue ground on staining with Mallory's method *(Figure 7)*. In some instances hyaline degeneration was noted in one part of the vessel, whereas other parts still revealed well defined sections staining perfectly with fibrin stain. In the remaining 6 cases, although no fibrinoid necrosis could be observed in the vessel walls, hyaline arteriosclerosis of the small arteries, arterioles and capillaries was always present *(Figure 8)*.

Histogenesis of Glomerulosclerosis and of the Hyalinosis of Small Arteries

Kimmelstiel and Wilson had already assumed that the glomerular lesion concurs with a primary sclerosis of the afferent arteriole. According to *Hall* [11], glomerulosclerosis would develop in consequence of sclerosis of the larger renal

arteries. Still, glomerulosclerosis may sometimes occur without a primary lesion of the afferent arteriole.

According to *Fahr* [7], hyaline thickening of the tunica propria of the renal tubules also occurs, the process being analogous to the glomerular degeneration. In some instances the basal membrane of Bowman's capsule, too, may undergo a hyaline thickening. It could be established in the course of the present, study that fibrinoid necrosis, as described to occur in the glomerular loopss

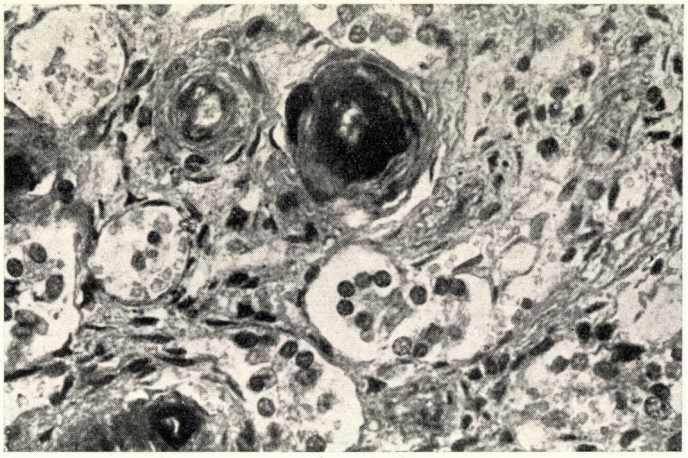

Fig. 7. Renal arterioles with thick wall and narrow lumen. Dark staining necrotic areas in the hyalinized arteriolar walls. Mallory's stain

occurs also in the basal membrane of the tubules, and in that of Bowman' capsule. Necrosis is followed by hyaline degeneration.

While *Stilling* and *Herxheimer* [23, 12] had erroneously considered hyaline arteriosclerosis as a lesion of the media, according to the present opinion, basen chiefly on the investigations of *Hesse* [13] and *Zakharyewskaya* [25], the lesiod develops in the intima, and destruction of muscle elements is but a secondary phenomenon. *Hesse* described an eosinophilic thickening of the subendothelial layer as the incipient stage of hyalinization. This author, however, did not study the histochemistry of his material. The so-called plasmatic imbibition is considered by *Zakharyewskaya* a characteristic lesion in small arteries.

Recently, in 1952, it has been suggested by *Duguid* and *Anderson* [5], that thrombosis is a factor which contributes to the development of diabetic arterial hyalinosis, by causing, in subsidiary manner, by way of recanalization, the arterial walls to thicken and undergo hyaline degeneration. In other cases, after having been organized, a mural thrombus would form a fibrous thickening

of the intima. We cannot accept that opinion, since it could be established that the origin of necrosis is not always subintimal. It is inconceivable that, after the parietal thrombus has been organized or the obturating thrombus recanalized, such a regularly shaped lumen should be formed in the axis of the artery as is found in hyaline arteriosclerosis. It is also improbable that thrombosis of the small arteries should simultaneously develop in widely different parts of the organism, and still less probable that all glomerular loops should be thrombosed at the same time, as is the case in glomerulosclerosis.

On the basis of our findings, we attribute the appearance of hyalinosis in the small arteries of diabetics, as also in patients with hypertension [6] or glomerulonephritis [3], to the fibrinoid necrosis of the vessel wall, in analogy with the process described above in connection with the development of glomerulosclerosis. This becomes especially obvious when a comparative study is made of the relationship between glomerulosclerosis and arterial lesions. As can be seen from Table I,the small arteries and the glomeruli display relatively identical lesions in the individual subjects; for instance, the most pronounced form of necrosis recorded in the small arteries of visceral organs occurred together with the most grave case of glomerulosclerosis (case No. 11). It is, therefore, suggested that the lesion of the glomerular capillaries is essentially identical with that of the capillaries, arterioles and small arteries of other organs.

Although the lesions of the glomerular capillaries and of the retinal arteries dominate the clinical picture, they must not be considered as isolated changes ; in order to understand them it is imperative that vascular lesions occurring in other parts of the organism should not be disregarded either. The fundamental changes characterizing Kimmelstiel—Wilson's syndrome cannot, therefore, be referred to the kidney alone. In our opinion, it is the generalized grave arterial degeneration which forms the basis of the syndrome and if it produces marked renal lesions, characteristic symptoms of glomerulosclerosis arise.

The view that the arterial lesion is a consequence of renal disease is unfounded, as we have observed some cases in which the vascular lesions were much more serious than those of the kidneys (Cases Nos. 6 and 10). Among 50 cases of diabetes recorded there were several in which grave hyalinosis and necrosis occurred in the small arteries though no glomerulosclerosis was present.

Pathogenesis of Glomerulosclerosis and of Arterial Lesions

When first describing the syndrome, *Kimmelstiel* and *Wilson* had stated that intercapillary glomerulosclerosis is characteristic of diabetes mellitus. Later, however, *Horn* and *Smetana* [16] examined whether glomerulosclerosis did not occur in cases other than diabetes mellitus. They have found that although the major part of the lesions observed, 59,1 per cent, occurred in diabetics, glomerulosclerosis may arise also in consequence of nephrosclerosis and glomerulo-

nephritis in patients who had no diabetes mellitus. Moreover, glomerulosclerosis was found in the kidney of a woman who had died after splenectomy in Banti's disease. It follows that although diabetes mellitus is the condition mostly responsible for glomerulosclerosis, the change may yet occur without diabetes.

The work of *Horn* and *Smetana* deserves special attention because it includes some cases dating from the time before the insulin era ; they show that glomerulosclerosis could develop also in patients who had not been treated with insulin, so that it would be a mistake to trace the lesion back to insulin therapy.

There are several pathological observations which may throw some light on the genesis of glomerulosclerosis. *Gsell* [10] found in 1946 hypertensive disease in a workman, 43 years of age, employed in the viscose industry, who had been exposed to carbon disulphide (CS_2) poisoning for 12 years. *Attinger* also described [1] the consequences of chronic carbon disulphide poisoning. *E. Uehlinger* [24], publishing the results revealed by autopsy and histological examination of 4 cases of glomerulosclerosis, stated that protracted carbon disulphide poisoning, unassociated with diabetes, produces renal lesions similar to those usually found in Kimmelstiel—Wilson's syndrome.

By removing 95 per cent of the pancreas, *Foglia*, *Mancini* and *Cadeza* [8] induced diabetes in rats. This was followed in from 2 to 12 months by glomerulosclerosis, thus proving that also the diabetes itself may give rise to the condition.

By administering to white mice 0,2 ml of a 10 per cent solution of urethane intraperitoneally twice a week, *Juhász*, *Baló* and *Kendrey* [18] produced glomerulosclerosis which led, in 6 months, to glomerulosclerosis and renal cirrhosis.

The experiments of *Rich*, *Berthrong* and *Bennett* [22] demonstrated that in rabbits pre-treated with horse serum lesions similar to diabetic glomerulosclerosis can be brought about by administering 7,5 mg of cortisone every day for two weeks.

Several data of literature point to the possibility that a change in the composition of serum proteins may play some part in the genesis of the fibrinoid necrosis of the glomerular capillary loops and arteries. According to *McManus* [20], the accumulation of pathological mucoprotein in the plasma of diabetics would be the cause of glomerulosclerosis and diabetic retinopathy. Other studies again indicate that pathological proteins, so-called paraglobulins, appear in the blood of patients developing Kimmelstiel—Wilson's syndrome. According to *Friedenwald* [9], an increase in the alpha-2 globulin fraction would be characteristic. *Randerath* [21] believes that diabetic glomerulosclerosis is really a vascular and glomerular nephrosclerosis combined with paraproteinaemic nephrosis.

Investigations in this direction are now in progress, and it is hoped that the results will contribute to a better understanding of diabetic glomerulosclerosis, and of the hyalinosis of small arteries.

Summary

Glomerulosclerosis, as described by Kimmelstiel and Wilson, was revealed by microscopical examination in 12 out of 50 cases of diabetes mellitus. Glomerular sclerosis develops from the fibrinoid necrosis of the glomerular capillary loops. In 6 out of the 12 cases, fibrinoid necrosis was present in the small arteries, arterioles and capillaries of the internal organs. In 3 of these cases, the transition from fibrinoid necrosis to hyalinosis could be observed, while hyalinosis of the small arteries of the organs was noted in 6 other instances.

A comparison of the glomerular change with arterial lesions in other organs has proved these two kinds of lesion to be of an identical character. The hyaline degeneration in both small arteries and glomeruli is due to fibrinoid necrosis.

Glomerulosclerosis, the fundamental lesion of Kimmelstiel-Wilson's syndrome, is but a partial manifestation of the arterial, arteriolar and capillary fibrinoid necrosis and hyalinosis generally observable in the organism of diabetics.

Although fibrinoid necrosis and hyalinosis of the small arteries occurs in other diseases as well (e. g. in hypertension or diffuse glomerulonephritis), the localisation and histological character of the diabetic arterial lesion will help to distinguish it from the general appearance of arteriosclerosis. A combined analysis of the clinical and histological changes makes it possible to diagnose diabetic angiopathy with a fair amount of certainty.

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СОСУДИСТЫЕ ИЗМЕНЕНИЯ ПРИ САХАРНОМ ДИАБЕТЕ И СКЛЕРОЗ ПОЧЕЧНЫХ КЛУБОЧЕК

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Р е з ю м е

Среди 50-и случаев сахарного диабета в 12 случаях удалось установить путем патогистологического исследования наличие склероза почечных клубочек, описанного Киммелштилом и Вильсоном. Склероз почечных клубочек исходит из фибриноидных некрозах петлей почечных клубочек. Среди этих же случаев в 6-и случаях мы нашли фибриноидный некроз мелких артерий, артериол и капилляров во внутренних органах. Среди последних в 3 случаях наблюдался переход фибриноидного некроза в гиалиноз. В 6-и других случаях мы нашли гиалиноз мелких сосудов.

Сравнывая изменения почечных клубочек с сосудистыми изменениями, встречаемыми в остальных органах, мы установили, что здесь речь идет об изменениях тождественного характера. Гиалиноз как мелких артерий так и почечных клубочек является последствием фибриноидного некроза.

Склероз почечных клубочек, представляющий основу синдромы Киммелштила и Вильсона, является частным явлением встречаемого вообще во всем организме фибриноидного некроза и гиалиноза мелких артерий, артериол и капилляров.

Хотя фибриноидный некроз и гиалиноз мелких сосудов встречается и при других заболеваниях (гипертоническая болезнь, диффузный гломерулонефрит), все-таки сосудистые изменения при сахарном диабете можно по расположению и по гистологическому характеру изменений отделить от общей картины артериосклероза. На основе совместной оценки клинических и патогистологических изменений сосудистые изменения при сахарном диабете являются четко ограниченной нозологической единицей.