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STUDIES ON THE PATHOGENESIS OF GLOMERULONEPHROSIS

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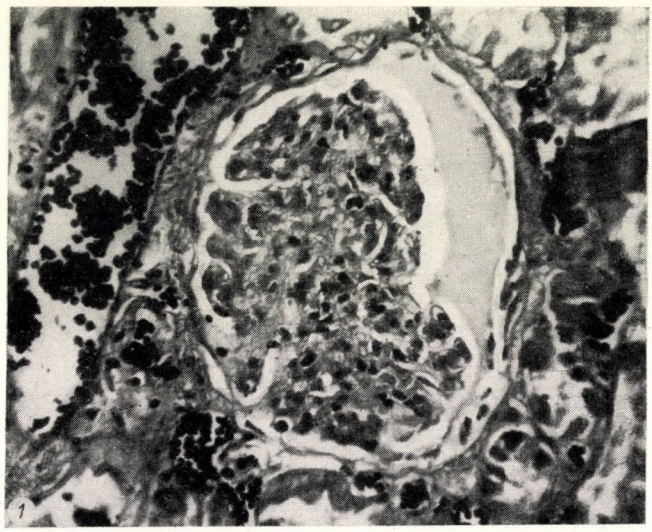
ZOLLINGER (23), analysing in detail the problem of spontaneous and experimental induced glomerulonephrosis, came to the conclusion that the condition occurs in association with a number of deseases, such as lipoid nephrosis, plasmocytoma, arthritis, renal rickets, amyloid nephrosis, diabetic glomerulosclerosis, jaundice, interstitial nephritis, various poisonings, cancer, etc. According to ZOLLINGER, in glomerulonephrosis there is a primary disturbance in protein metabolism ; pathological proteins appear in the blood and infiltrate the glomeruli. Lesion of the basement membrane of the glomeruli occurs secondarily. The histological appearance would indicate a degenerative-infiltrative change in the glomerular loops and intercapillary tissues which in the chronic stage becomes associated with capillary sclerosis. MUNK [17] gave the term serous imbibition to this homogeneous thickening of the basement membrane and intercapillary tissues.

Experimental

(i) In the first part of our studies the kidneys of 110 subjects died with tumour were examined. Of the 110 subjects 10 were 0—30 year old, 75 were between 30 and 60, and 25 above 60, years of age. Cancer of different organs occurred in 85 subjects ; in 25 other tumorous changes were found, including various forms of sarcoma and leukaemia.

Gross examination of the kidneys showed no significant change. Microscopic lesions characteristic of glomerulonephrosis were detected in 52 out of the 110 cases. The kidneys were stained with haematoxylin-eosin, Heidenhain's azan, Endes' trichrome, with van Gieson's stain and with McManus' periodic acid Schiff-reaction. In most of the glomeruli, swelling of the epithelial and intercapillary cells and thickening of the basement membrane of the glomeruli (Fig. 1), as well as widening of the intercapillary spaces (Fig. 2) and appearance of protein in Bowman's capsule were observed. Some glomeruli were atrophied. There was hyalin droplet degeneration in the tubular epithelium.



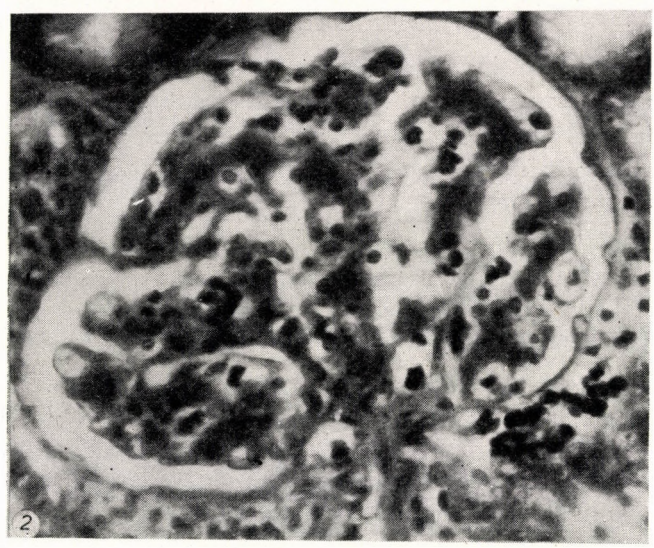


Fig. 1. Thickening of the glomerular basement membrane; protein in Bowman's capsule (Heidenhain's azan stain)

Fig. 2. Protein imbibed and expanded intercapillary spaces (Heidenhain's azan stain)

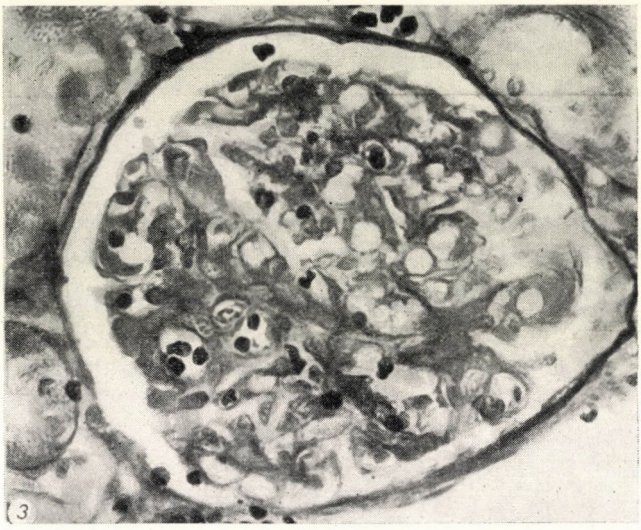
In connection with these changes, the question arose whether some other disease of the kidneys was present. Since most of the kidneys examined originated from subject above 30 years of age, the changes due to glomerulonephrosis had to be differentiated from those of malignant nephrosclerosis, arteriolosclerosis and primary senile degeneration of the glomeruli. According to ZOLLINGER [23], differentiation of glomerulonephrosis from the other processes presents no particular difficulty. From malignant nephrosclerosis, differentiation is made on the basis of arteriolar changes and the presence in this condition of inflammatory glomerular alterations. From the arteriolosclerotic kidney, on the basis of localization. (Glomerular changes associated with arteriolosclerosis, namely, develop in consequence of ischaemia, due to occlusion of the arterioles. Collapse of the glomerular loops occurs, therefore, first, and thickening of the basement membrane secondarily; the infiltrative component being absent, thickening of the basement membrane is slight, the membrane rather becomes tortuous. The characteristic localization will help to evade difficulties in differential diagnosis.) Finally, glomerulonephrosis may easily be differentiated also from the primary senile degeneration of the glomeruli described by KIMMELSTIEL; this condition is first of all characterized by the widening of intercapillary spaces, and thickening of the basement membrane occurs only later. ZOLLINGER observed that the different cellular elements fail to take part in this process. Moreover, the changes affect only part of the glomeruli in the subcapsular zone, whereas in glomerulonephrosis the process is diffuse.

Material showing the just discussed signs of malignant nephrosclerosis, arteriolosclerotic kidney, or primary senile degeneration of the glomeruli, has not been included in our studies.

(ii) In the second part of the studies the kidneys of 40 tumorous rats were examined. Tumour was induced by benzpyrene, administered in doses of 1,5 mg every third day, all in all 4 times. The tumour, fusocellular and polymorphocellular sarcoma, developed usually within 90 days.

Gross changes in the kidney were insignificant. A histological pattern corresponding to glomerulonephrosis occurred in 15 out of the 40 animals; in these the basement membrane of the glomeruli was thickened (Fig. 3), the intercapillary spaces were widened, protein was present in Bowman's capsule, with hyalin droplet degeneration in the tubular epithelium and some hyaline casts in the lumen.

On the basis of the findings in the two series, it has been ascertained that both in tumorous subjects and in tumorous rats glomerulonephrosis may develop. Since, according to ZOLLINGER's [24] view, protein disintegrating in the organism is responsible for that condition, further experiments were carried out in rabbits by feeding them various types of protein and examining whether or not changes developed in the kidney.



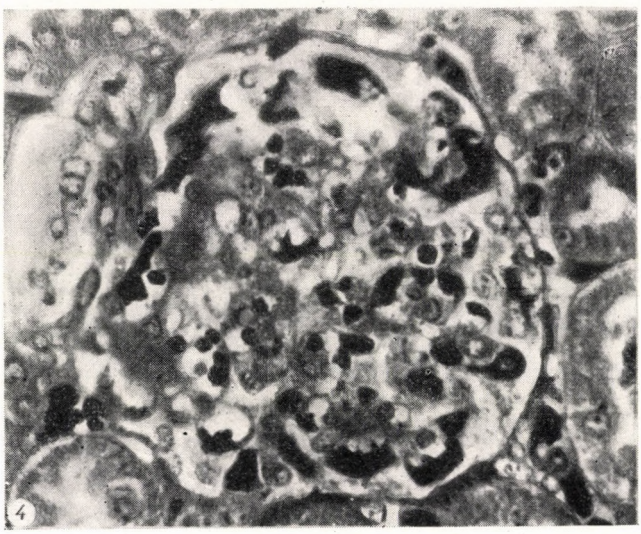


Fig. 3. Thickening of the glomerular basement membrane and expansion of the intercapillary tissues in rat kidney (Heidenhain's azan stain)

Fig. 4. Thickening of the glomerular basement membrane and protein in Bowman's capsular spaces in rabbit kidney (Endes' trichrome stain)

(iii) 37 rabbits ranging in weight from 2500 to 3500 g were used in the experiments. The animals were divided into 4 experimental groups.

(a) 12 animals belonged to this group. They received through a stomach tube daily 7 g of dried egg white dissolved in water. One animal was given that dose 6 times ; one, 10 times ; two, 17 times ; one, 50 times ; three, 90 times ; and three animals, 100 times, always 7 g daily.

(b) 10 rabbits belonged to this group. They were administered 3—5 ml of native egg white daily by the intravenous route. The egg white was separated from the yolk under aseptic conditions and diluted 1 : 1 with sterile physiological saline. From the diluted egg white were administered 3—5 ml.

Duration of treatment and amount of intravenously injected egg white was as follows. 1 rabbit, 7 times 3 ml ; 2 rabbits, 11 times 3 ml ; 2 rabbits 16 times 3 ml ; 2 rabbits, 35 times 5 ml ; 3 rabbits, 56 times 5 ml.

(c) This group contained 10 rabbits daily, treated intravenously with 5 ml casein solution. The solution was prepared by diluting 100 mg casein in 5 ml sterile physiological saline. 3 animals were sacrificed after 10 injections; 3 animals after 20 injections ; 2 animals after 30 ; and 2 after 40 injections.

(d) 5 rabbits constituted this group. They were treated intravenously with 3 ml of normal horse serum daily. Histological examination was carried out in 3 animals after 11 injections, in 1 animal after 14 ; and in 1 animal after 16 injections.

The same type of changes developed in the kidneys of the animals, whether they belonged to group a., b., c., or d., so they will be discussed together.

Gross examination of the kidneys showed no significant changes. Under the microscope, however, characteristic lesions were detected. The earliest change was the nuclear swelling of epithelial cells. It developed after 6 to 7 treatments, at a time, when the glomerular basement membrane was not yet thickened. After 11 injections there appeared thickening of the glomerular basement membrane (Fig. 4) ; widening of the intercapillary spaces ; protein in Bowman's capsule, sometimes globular in form ; hyaline droplet degeneration in the tubular epithelium ; hyalin casts in the lumen of the tubules ; and interstitial oedema. The changes grew more severe with continuation of the treatment, especially the widening of the intercapillary spaces and the thickening of the glomerular basement membrane. These two became gradually more marked between the 11th and 20th treatments. The glomerular basement membrane stained blue or purplish red with Heidenhain's azan, a violet blue or pale red with Endes' trichrome, yellow with van Gieson's method and gave a positive McManus periodic acid Schiff reaction. Atrophied glomeruli were also present in the animals treated for the longest time.

Discussion

In the experiments, glomerulonephrosis was observed to develop in tumorous subjects, tumorous rats and also in rabbits treated with various kinds of foreign protein. SÜMEGI [22], too, is of the opinion that changes similar to glomerulonephrosis develop in rats with cancer. Many authors have succeeded in inducing glomerulonephrosis experimentally : AHLSTRÖM [1] by the injection of Dick toxin into the renal artery ; PATRASSI [18] by the injection of diphtheria toxin, and GEISER [11] by intraperitoneal administration of trypsin, to dogs ; KRYLOW [14] by feeding frogs with a high-protein diet for 180—360 days ; ELLENBECK [7] by Bence—Jones protein ; and ZOLLINGER [27] by pig and horse serum.

Several authors have discussed the relation of glomerulonephrosis and glomerulonephritis. Some of them strictly separate the two processes. LÜDERS [16] and ZOLLINGER [24] claim that, though in chronic glomerulonephrosis an additional inflammatory process may take place in the glomeruli, still it is incorrect to consider the condition as of inflammatory nature, and glomerulonephritis must be rigorously distinguished from glomerulonephrosis. ZOLLINGER [23] further supports this conception by the fact that hypertension is rare in glomerulonephrosis but quite common in nephritis. He is of the opinion that hypertension occurring in cases of glomerulonephrosis is of extrarenal or, at least, of extraglomerular, origin. In contrast to this, some authors report of increased cellularity in glomerulonephrosis. RANDERATH [21], e.g. noted an increase in epithelial cells beside thickening of the basement membrane while CORONINI [6] described nuclear proliferation. PATRASSI [18] observed nuclear proliferation, thickening of the basement membrane, and even loop-necrosis as a response to large doses of diphtheria toxin. Administration of smaller doses of the toxin resulted in thickening of the basement membrane as a dominant change. ROULET and RUTISHAUSER [21] stated that in glomerulonephrosis dysoria is the primary change and a serous inflammatory process in the glomeruli takes place only at a later period, bringing about, finally, sclerosis of the glomeruli. HENRICH [13] and CORONINI [6] hold the same view, but ZOLLINGER [27] considers it to be incorrect. Most of the investigators do not regard nephrosis to be an individual disease, only as a variation of glomerulonephritis. ALLEN [2], BELL [3], BOYD [5], RÓNA [20], GÖMÖRI [12], claim that nephrosis belongs to the glomerulonephritis group and not into that of degenerative kidney diseases. According to ENDES and TAKÁCSI-NAGY [8], nephrosis and nephritis are different reactions to one and the same effect and it depends on age as well as on the reacting ability of the organism whether nephrosis, of which recovery is possible, or severe, progressing nephritis, develops. This statement was supported by animal experiments, since administration of nephrotoxin resulted glomerulonephritis in some cases whereas in

others nephrosis was produced. FARKAS [9] claims that in toxic nephrosis a severe glomerular lesion takes place. In her studies, BEREGI [4] observed that in experimentally induced glomerulonephritis thickening of the basement membrane may precede nephritis.

It has been demonstrated in the present studies that, associated with protein decomposition or due to protein treatment, glomerulonephrosis develops. No glomerulonephritis was found in the animals. According to data in the literature, however, administration of protein for a long time produces glomerulophritis. MCLEAN, FITZGERALD, YOUNGHUSBAND and HAMILTON [15] observed acute, subacute, and chronic glomerulonephritis to develop in rabbits after administration of 0,5 ml horse serum daily for 3 to 13 months, but they did not examine the animals for the presence of early changes. Our present experiments did not involve such a longlasting treatment, since we hold the afore-mentioned results fully convincing.

The literary data cited above raise the question, whether or not an allergic process is brought about by the protein. RICH and GREGORY [19] succeeded in producing periarteritis nodosa with a single large dose of horse serum. Many authors explain this phenomenon by the fact that a single dose of the substance suffices to bind enough serum to the cells to allow autoantigen production. GAÁL [10] reported the case of a 43 years old woman who, without ever having previously been treated with serum, was given an injection of tetanus serum, and 9 days later died of serum sickness in the course of which acute glomerulonephritis developed. The systemic autoaggressive mechanism was held responsible for the morphological changes in different organs. All these point to the important role of allergic mechanisms in the development of renal lesions induced by protein intake. We are of the opinion that no rigorous differentiation between nephrosis and nephritis can be made. Further investigations are necessary to demonstrate a median phase between the two conditions.

Summary

The kidneys of 110 subjects died with tumour and 40 tumorous rats were examined. Both in the human subjects and in the animals a histological pattern characteristic of glomerulonephrosis was found. Since data in the literature claim protein decomposition products to have a role in the development of the disease, various types of protein were administered to animals. 12 rabbits were fed egg white through a stomach tube ; 10 rabbits were given casein intravenously ; 10 rabbits received native egg white ; and 10 rabbits were intravenously injected various amounts of normal horse serum for different periods of time. As a result, changes corresponding in every respect to those of glomerulonephrosis were detected

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ИССЛЕДОВАНИЯ В СВЯЗИ С ПАТОГЕНЕЗОМ ГЛОМЕРУЛОНЕФРОЗА

Е. БЕРЕГИ, ДЬ. ДЕВАИ и Ш. КОВАЧ

Авторы исследовали почки 110 страдающих опухолью лиц, далее почки 40 пораженных опухолью крыс, и установили, что у вскрытых лиц и у крыс образовалась характерная для гломерулонефроза гистологическая картина. Согласно литературным данным в возникновении гломерулонефроза важную роль играет распад белков, и поэтому авторы давали в дальнейшем подопытным животным различные белки : они вводили 12 кроликам через зонд яичный белок, 10 кроликам они вводили нвутривенно казеин, 10 кроликам внутривенно — нативный яичный белок и 5 кроликам внутривенно — нормальную лошадиную сыворотку в различных количествах и в течение различного времени. На основании гистологического исследования они выявили измения, которые во всех отношениях были подобны гломерулонефрозу.

ÜBER DIE PATHOGENESE DER GLOMERULONEPHROSE

E. BEREGI, GY. DÉVAI und S. KOVÁCS

Es wurden die Nieren von 110 tumorbefallenen Personen, sowie von 40 tumorbefallenen Ratten untersucht und hierbei sowohl in Menschen wie auch in den Ratten ein für die Glomerulonephrose charakteristisches histologisches Bild festgestellt. Laut literarischer Daten spielt der Eiweisszerfall in der Entstehung von Glomerulonephrose eine bedeutende Rolle. Aus diesem Grunde verabreichten die Verfasser den Versuchstieren verschiedene Eiweisse : 12 Kaninchen wurde durch Sonde Eiereiweiss, 10 Kaninchen i. v. Kasein, 10 Kaninchen i. v. natives Eiereiweiss und 5 Kaninchen i. v. normales Pferdeserum eingeführt. Bei der histologischen Untersuchung wurden der Glomerulonephrose in jeder Beziehung ähnliche Veränderungen festgestellt.

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