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THE PATHOGENESIS OF MALIGNANT HYPERTENSION

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Volhard and *Fahr* considered nephrosclerosis as a primary affection of the kidneys and the concomitant hypertension as a corollary of «renal disease» [32]. The clinical and morphological aspects of the condition suggest a differentiation between a «*benign*» and a «*malignant*» form of nephrosclerosis. *Fahr* [15] described the benign form as characterized by sclerosis of the renal arteries and the malignant one by necrotizing and inflammatory arterial changes. This concept was further developed by *Schürmann* and *MacMahon* [30] who also reported on a specific arteriolar change. While their definition of the *morphological* characteristics of nephrosclerosis is still valid, present views markedly differ from earlier ones as to the origin of the pathological changes involved. The results of some, mainly animal experiments have tended to show necrosis of the arterioles, said to be incident to the condition, to be determined solely by the high diastolic pressure ; other authors again assign some measure of responsibility to other factors such as uraemia, destruction of renal tissue, etc.

At present, nephrosclerosis is considered a product of essential hypertension instead of a primary renal disease. The customary division of hypertensive disease is into two broad types, a benign and a malignant form, — the first marked by a slow protracted course with a bare 10 per cent mortality from renal insufficiency, the latter progressing at a rapid rate with death, mostly as a result of uraemia, generally supervening in a matter of 2 to 3 years. Apart from this form of primary malignancy, there is a «malignant phase» of the benign form, meaning cases with the progress abruptly accelerating and with the appearance of symptoms usually associated with the malignant form. Following the lead of *Lang* [22], benign hypertension is now looked upon as a neurogenic affection with a merely secondary involvement of the kidneys which, accordingly, are only indirectly concerned in the maintenance of the hypertensive state. On the other hand, the pathogenesis of malignant hypertension is still an open question. *Abrikosov* [1], *Tarayev* [31], *MacMahon* and *Pratt* [25], *Kimmelstiel* and *Wilson* [21] all state that, as regards pathogenesis, there is a definite qualitative difference between the two varieties of hypertensive disease. *Lang* [22], *Anitchkov* [4], *Byrom* and *Dodson* [10], *Picker-*

ing [27] and *Gömöri* [17], in their turn, consider them as the milder and severer forms of the same disease, differing in degree only. Following *Derow* and *Altshule* [12], there is a recent tendency to regard malignant hypertension, instead of a separate entity, a clinical syndrome resulting either from primary hypertensive disease or from some renal affection. On the basis of our findings, *Gömöri* [18, 19] in his lectures held in the Prague Cardiological Society, and at the Gottwaldov Congress on Hypertension, also adopted this interpretation. Since the necrotizing vascular changes peculiar to malignant nephrosclerosis have been recorded exclusively on autopsy material, there might be some ground for regarding them as characteristic of only the terminal uraemic stage of hypertensive disease.

The present study was devoted to the question of the pathogenetical relationship between benign and malignant hypertension, further to the connection between malignant and benign hypertension on the one hand and malignant benign nephrosclerosis on the other. It should be noted that the terms malignant and benign hypertension are used in the clinical sense, while the words malignant and benign nephrosclerosis cover purely morphological findings. The adequate answer to the question must accrue from a combination of clinical investigation with methods of pathological anatomy. This has been made possible by recent clinical examinations of increased exactitude, by means of which malignant hypertension may be diagnosed before any disturbance in renal function has set in and further by renal biopsy which allows histological information to be acquired about its early stage, and not only on the terminal phase consisting in renal insufficiency. We made therefore a histological study of biopsy samples in the early stage of malignant hypertension, while its terminal stage was examined on necropsy material. Moreover, we have analyzed vascular changes incident to malignant nephrosclerosis.

I. Biopsy material

The first part of the present paper is devoted to the histology of the early stage of malignant hypertension. Material was obtained by biopsy performed during thoracolumbar sympathectomy in hypertensive patients. It took the triple criterion of speedy progress, high diastolic pressure and grave changes in the ocular fundus to establish a diagnosis of malignant hypertension. Diastolic pressure was considered high at or above a permanent level of 140 mm mercury. In addition to the characteristic hypertensive fundus, there had to be retinal and papillary oedema. The cases under review number 12. Primary malignant hypertension was diagnosed solely in cases with a history dating back to less than 2 years (10 in all), while 2 out of the 12 patients presented the aspect

of a malignant phase supervening on a benign condition of long standing. All the subjects concerned showed a normal renal function, a satisfactory concentrating capacity and a normal glomerular filtration rate.

Glomerular filtration was estimated from the endogenous creatinine clearance (C_K); in certain cases, the volume of plasma clearance (C_{PAH}) and the filtration fraction were also determined.

Biopsy was performed by *Castleman* and *Smithwick*'s [11] method, consisting in the removal from the kidney of a wedge-shaped strip 1,5 to 2 cm in length and 1 cm in width and depth. In *Castleman* and *Smithwick*'s [11] experience, confirmed by our own findings *(Endes* and *Takács-Nagy)*, this provides suitable material for judging the state of the kidney. Staining was performed with Sudan III, haematoxylin-eosin, Van Gieson's elastic stain and Heidenhain-type Azan.

The age of our 10 patients suffering from primary malignant hypertension ranged from 27 years to 50 years, with six over and four below 40 years. The glomerular filtration rate was between 72 and 131 ml/min in 9 cases, and 60 ml/min in one. Plasma clearance, determined in 6 of the cases, was invariably found below normal (between 325 and 416 ml/min in five cases, 325 ml/min in one case). The first hypertensive disorder had appeared from ½ to 2 years, the first rise in blood pressure from 2 months to 2 years before admission. We had two cases of benign hypertension passing into a malignant phase, where the patients' age was 30 and 50, respectively; the glomerular filtration rate was 78 and 63 ml/min, respectively; in one case the plasma clearance was 300 ml/min. Hypertension had supervened for 4 to 10 years.

According to our earlier system of classification *(Endes* and *Takács-Nagy* [13], we divided the histological changes observed into three groups. The term mild (+) has been used to denote cases with lamellar fibroelastosis in the arteries, minute scars, hyaline glomeruli, with merely sporadic occurrence of arteriolar hyalinosis. Medium (++) cases exhibited an increased frequency of hyaline-lipoid infiltration of the arterioles, which, however, generally confined itself to a sector of the vascular wall, and was of a patchy character. The term severe (+++) was applied to cases exhibiting frequent and well-marked infiltration of the arterioles mostly affecting the whole periphery of the vascular wall. According to this classification, 5 out of our 12 cases of malignant hypertension were rated as severe, with 2 out of the 5 representing the malignant phase of benign hypertension, 5 as medium and 2 as mild. In no case, however, did we observe any inflammatory necrotising vascular changes specific to malignant nephrosclerosis. The weight of our results is borne out by *Castleman* and *Smithwick*'s [11] findings who, have neither found arteriolar necrosis in the biopsy material of any of their 14 cases of malignant hypertension.

Apart from the described lipoid-hyaline infiltration of the intima, we succeeded on several occasions in demonstrating in the muscle layer of the renal arterioles *degenerative patches* with Azan staining a homogeneous red. We attach some importance to this finding, because literature is lacking in evidence on the degenerative changes of the media, although *the persistent*

contraction of the arteriolar musculature is one of the dominant factors in the pathomechanism of hypertension.

A comparison of our material with the biopsy records from 64 cases of benign hypertension shows by and large the same changes in the clinically manifest benign cases, the only mark of malignity lying in the greater frequency of grave and medium, and the comparative rarity of mild symptoms. In none of the malignant cases in which biopsy had been performed did the subsequent post-mortem examination reveal any signs of malignant nephrosclerosis. Accordingly, it is not directly demonstrable that the initial stage of those hypertensive cases which terminate with typical malignant nephrosclerosis show none but the degenerative arteriolar changes encountered in benign hypertension, nor that the difference between the two forms is merely a quantitative one. In four cases could biopsy be supplemented by subsequent necropsy. In two of them, death had supervened in the post-operative state, as a result of intercurrent disease, while the other two ended in renal insufficiency brought about by some other factor associated with existing hypertension. None showed histological evidence of malignant nephrosclerosis. Yet the identity of the early tissue changes encountered in benign hypertension with those developing during the malignant form must be clear from those biopsied cases which, though advanced to such an extent as to be attended by a high diastolic pressure and with grave fundus symptoms, were nevertheless found to exhibit none but degenerative arteriolar changes in the kidneys, without the signs of necrosis. The histological symptoms of nephrosclerosis are, accordingly, developed only during the final stage of hypertensive disease.

II. Autopsy material

18 cases were autopsied, 8 had been clinically diagnosed as malignant hypertension, 6 out of the 8 showing, moreover, the characteristic histological aspect of malignant nephrosclerosis, with inflammatory and necrotizing vascular changes. In 2 cases, histological examination showed only benign nephrosclerosis ; the patients had died shortly after sympathectomy without symptoms of renal insufficiency. In these 8 typical cases we shall not go into details. Another 10 cases, with clinical signs of primary malignant hypertension or hypertensive disease passing into malignancy, were found to exhibit kidney changes of a different nature, attended or unattended with symptoms of malignant nephrosclerosis.

We have invariably worked up the kidneys, parts of the heart, the spleen, the liver, the pancreas, the adrenal glands, and a section of the medulla and the basal ganglia; in certain cases also the intestinal wall and the testicles. Frozen sections were stained for fat with Sudan ; fixed ones with haematoyxlin-

eosin, van Gieson's elastic, stain, Heidenhain's Azan ; in some cases Weigert's fibrin staining and Foot's silver impregnation was also carried out. For studying hypertensive arterial changes and for simultaneous demonstration of all vascular lesions, our modification of Mallory's MPH method (phosphotungstic acid haematoxylin) with Azan [14a] has proved the best. In the following we give a brief clinical and morphological report on our cases :

(i) L. U. a man 37 years of age, with a history dating back to 2 years. Essential hypertension with adequate renal function was demonstrated six months before death. A few weeks later his state deteriorated, haemorrhages and degenerative spots developed in the fundus, followed by oedema of the retina and the papilla. At this stage, the blood pressure was 260/180 and 250/150 mm. mercury, NPN amounted to 174 mg per 100 ml. The patient died with uraemia. The heart weighed 470 g, the kidneys 240 g. There were cerebral oedema, minute haemorrhages in the right lentiform nucleus, signs of malignant nephrosclerosis in the kidneys. Necrosis of certain larger interlobular arteries was found, extending to the renal tissue, and surrounded by a peculiar granulation tissue with giant cells (Fig. 1), corresponding to the granulomatous arteritis described by Allen [2] and others, — a condition supposed to be of allergic origin. Signs of inflammation in numerous glomeruli, marked proliferation of the capsular epithelium, with occasional crescents, were present. Alkaline phosphatase activity was maintained in the hypertrophied tubules, while it was absent from the distended tubuli lined with low epithelium.

Accordingly, there were clinical symptoms of hypertension and, histologically, malignant nephrosclerosis accompanied by arteritis of unknown (allergic?) origin, which must no doubt have done its part in accelerating the progress of the disease in the last half-year.

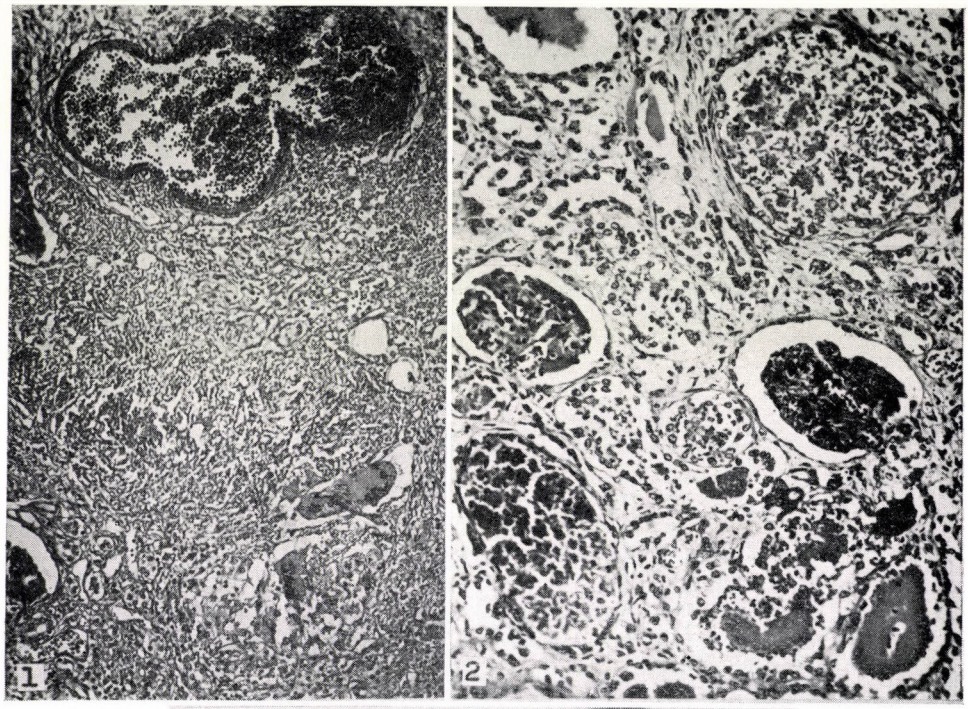
(ii) B. K., a man 39 years of age, had had hypertension for three years. 10 months before death his blood pressure was between 220/150 and 200/140 mm. mercury. He had been able to work until 3 weeks before death, when he was taken ill with tonsillitis and a peritonsillar abscess. Sudden deterioration of his state ensued and retinal and papillary oedema developed. C_K was 4 ml/min. Death occurred from uraemia.

Autopsy performed at a provincial hospital disclosed cardiac hypertrophy, slightly enlarged kidneys with minute abscesses and haemorrhages. The kidneys, which alone were available for histology, showed severe purulent nephritis with multiple abscess formation ; in the remaining parts malignant nephrosclerosis was present with vascular changes suggestive of long-standing hypertension.

The purulent nephritis of infectious origin complicated by severe hypertension increased the pace of the progress and closely imitated malignant hypertension. Histologically, there was malignant nephrosclerosis together with purulent nephritis.

(iii) I. M., a man 23 years old, had hypertension since a year, with a blood pressure of 235/150 and 230/140 mm. mercury. There were only vascular symptoms in the fundus. C_K amounted to 135 ml/min. Two and a half months before admission unilateral Smithwick's operation was carried out, together with renal biopsy. Subsequently a febrile condition of unknown origin developed, with a rise in blood pressure to 250/170 mm. mercury and with retinal and papillary oedema. NPN was 204 mgr per 100 mgr. Death ensued from uraemia.

The heart weighed 540 mgr, the kidneys 360 g. Marked hypertensive vascular changes but no signs of inflammation occurred in the kidney specimen removed with biopsy $2\frac{1}{2}$ months before. At autopsy, the kidneys exhibited pronounced acute inflammatory changes beside vascular ones typical of benign nephrosclerosis. Diffuse lympho- and leucocytic infiltration, and interstitial oedema were present. The tubules were distended, full of leucocytes, red blood corpuscles and homogeneous casts (Fig. 2). In the glomeruli, proliferation of the capsular epithelium, segmentation, adhesive glomerulitis were seen, and at places also crescents.



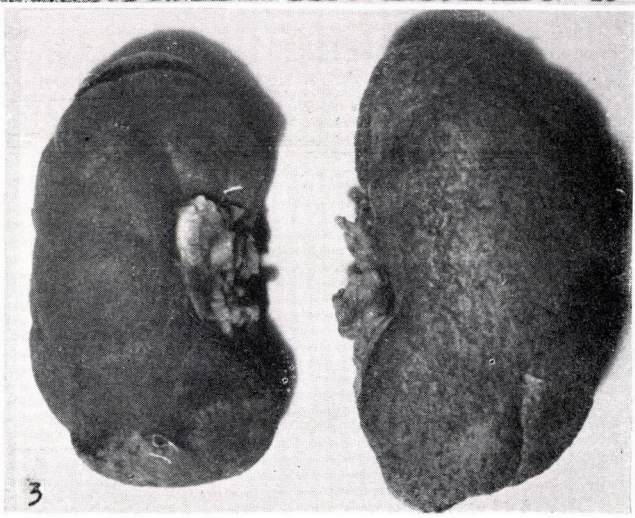


Fig. 1. Necrotic artery, periarterial granulation with giant cells (Case 1)
Fig. 2. Vastly distended tubuli full of leucocytes. The dark spots mark the calcification of the tubular epithelium. Increased and inflamed interstitium, atrophied glomeruli (Case 3)
Fig. 3. Macroscopic view of the larger left and the smaller right kidney. The surface in the lower part of the right kidney is smooth (Case 6)

In this case the malignant hypertensive condition developed in the association of the existing hypertension with an acute inflammation bringing about rapid deterioration of renal function. Sings of malignant nephrosclerosis were absent. The case called attention to an eventual relation between the acute, mainly interstitial-tubular inflammation, and the sympathectomy previously performed.

(iv) J. B., a woman 42 years of age had had an elevated blood pressure since pregnancy pyelitis contracted 12 years ago, and hypertensive complaints for the last 2 years. The blood pressure was between 260/180 and 240/150 mm. mercury. There were retinal and papillary oedema, C_K was 10 ml/min. In the urinary sediment, 200 leucocytes per field were found. NPN was 86 mg per 100 ml. Death ensued from uraemia.

The heart weighed 420 g. A «patchy spleen», cerebral oedema, recent and chronic encephalomalacia were found at autopsy. The left kidney weighed 40 g. It was very small and scarred and displayed chronic pyelonephritis. The right kidney weighed 130 g and exhibited no sign of pyelonephritis. In both kidneys there were hypertensive arterial changes and even malignant nephrosclerosis with necrosis of the arterioles and arteriolitis.

The underlying affection was a chronic pyelonephritis in one kidney, associated with hypertension. Histology revealed changes consequent upon long-standing hypertension, along with symptoms of malignant nephrosclerosis also present in the normal-sized kidney without being any more pronounced.

(v) Mrs. Gy. B., a female patient 40 years of age had had albumen and pus in the urine since a pregnancy pyelonephritis 14 years before. She had had hypertensive complaints for the last two years, and repeatedly haematuria. Her blood pressure was 250/160 mm. mercury. C_K was 22 ml/min. NPN amounted to 72 mg per 100 ml. Death ensued from cardiac decompensation.

The heart weighed 600 g. A «patchy spleen» and cerebral oedema were present. The left kidney weighed 245 g. The right kidney was scarred and shrunken and weighed 85 g. Histology revealed in the right kidney chronic scarred pyelonephritis, necrosis of the arterioles, periarteriolar granulomas beside earlier hypertensive vascular changes. In the left kidney there was no pyelonephritis and vascular changes were like on the other side.

The case presented scarred pyelonephritis of long standing in one kidney, associated with hypertension. Histologically both kidneys had been affected with malignant nephrosclerosis.

(vi) E. W., a man 53 years of age with a two and a half years history of hypertension. Blood pressure a year before was 230/140 mm mercury. It was later lowered by Vegolysen treatment, but afterwards it rose again to 280/170 mm. mercury. Retinal oedema was present ; C_K was 42 ml/min ; there was hyposthenuria ; NPN was 70 mg per 10 ml. Death was due to circulatory insufficiency.

The heart weighed 590 g. The left kidney, weighing 165 g, had a diffusely granular surface, yellowish red in colour. The right kidney weighed 120 g : the upper fifth of its surface was like that of the left kidney, the rest almost entirely smooth, livid (Fig. 2). Histology showed a chronic cicatrizing interstitial inflammation in the smooth part of the right kidney, localized mainly at the subcapsular zone of the cortex, but occurring also at deeper levels, in streak-like foci (Fig. 4). In the left kidney and in the upper part of the right one there were wedge-shaped cortical scars with chronic inflammatory infiltration, but the histological difference from the smooth part was hardly more than quantitative. Also hypertensive vascular changes occurred without signs of arteriolar necrosis. The vascular changes in the smooth part of the right kidney were considerably less marked and less frequent than those near the upper pole.

In both kidneys, chronic interstitial inflammation was found, localized in the right kidney to the subcapsular zone in the lower fourfifth of the organ.

The rest of the kidneys corresponded histologically to the picture of benign nephrosclerosis. The process was similar to experimental hypertension brought about by unilateral kidney compression. C inically, the case was one of malignant hypertension, but at autopsy no malignant nephrosclerosis was found.

(vi/a) A case where biopsy was performed presented a comparable histological aspect. E. V., a woman 23 years of age, presenting very grave malignant hypertension with a blood pressure fixed at 240/160 mm mercury. There was papillary oedema of 5 dioptries on the right side and 6 dioptries on the left side. C_K was 72 ml/min. The urine was slightly opalescent and contained 8 to 10 leucocytes in the sediment. In the subcapsular layer of the renal biopsy specimen of chronic interstitial inflammation and scarring were found, with numerous hyaline glomeruli. There was no sign of hypertensive vascular changes in the arterioles ; on the other hand, the arterioles of the sympathetic ganglia removed at the same time displayed very grave necrosis.

It was thought that in this case the malignant hypertension was, as in Page's experimental perinephritis, due to renal ischaemia. Since, however, the small specimen obtained with biopsy did not allow to ascertain the extent of cicatrization in the marginal cortical zone, the question had to be left unanswered.

(vii) Mrs. S. B., a woman 42 years of age. Hypertension had been discovered accidentally four years before, but symptoms did not appear until half a year ago. Her blood pressure was 250/130 mm. mercury, she had retinal and papillary oedema, and an Addis' count of 100 million erythrocytes, and 13 million leucocytes. C_K was 63 ml/min., NPN 144 mg per 100 ml. With the grave fundus symptoms pointing to malignant hypertension and the urine sediment to inflammatory nephropathy, indication for sympathectomy with renal decapsulation was set and the operation performed. Six days later the patient died from bronchopneumonia and pleuritis.

The heart weighed 480 g, the kidneys 250 g. They had a fine granular surface, the cortex was yellowish. Histology revealed hypertensive vascular changes without arteriolar necrosis and chronic proliferative membranaeous glomerulonephritis.

Clinically, malignant hypertension was diagnosed but, on the basis of the high Addis'count, an inflammatory process had also to be considered. Post mortem chronic nephritis associated with signs of benign nephrosclerosis was found.

(viii) Gy. N., a man 46 years of age had a two-year history of hypertensive disturbances, with a blood pressure between 210/170 and 200/145 mm. mercury, and degenerative spots and haemorrhages in the fundus. C_K was 16 ml/min.

The heart weighed 510 g. the right kidney and the ureter were missing, the 1 cm long right renal artery ended blind. The left kidney weighed 210 g, its surface was granular, the cut surface displayed some colloid cysts localized mainly in the medulla. Histology of the kidney revealed apart from cysts of varying size, chiefly confined to the medulla, chronic inflammatory, cicatrized foci, and grave hypertensive vascular changes, with no signs of necrosis.

The defective development of the right kidney and the few medullary cysts in the left kidney might have aggravated the hypertension, similarly as in Goldblatt's experiment, or even have been the cause of the condition. Clinically, the case seemed to be one of malignant hypertension, but at autopsy no malignant nephrosclerosis was found.

(ix) Mrs. J. W., a woman 58 years of age has had diabetes and hypertension for five years. On admission her blood pressure was 270/150 mm. mercury. Ophthalmoscopy showed protruding papillae, oedema of the macular region, degenerative spots, slight retinal haemorrhages. The absence of oedema suggested, in spite of similarities with Kimmelstiel—Wilson's syndrome, malignant hypertension. Death occurred from uraemia.

The heart weighed 500 g. There was bilateral confluent bronchopneumonia. The kidneys weighing 140 g displayed numerous hyaline glomeruli and *Kimmelstiel—Wilson* bodies staining with Sudan and fibrin-stain. Severe changes were found in the arteries and arterioles. In the latter,

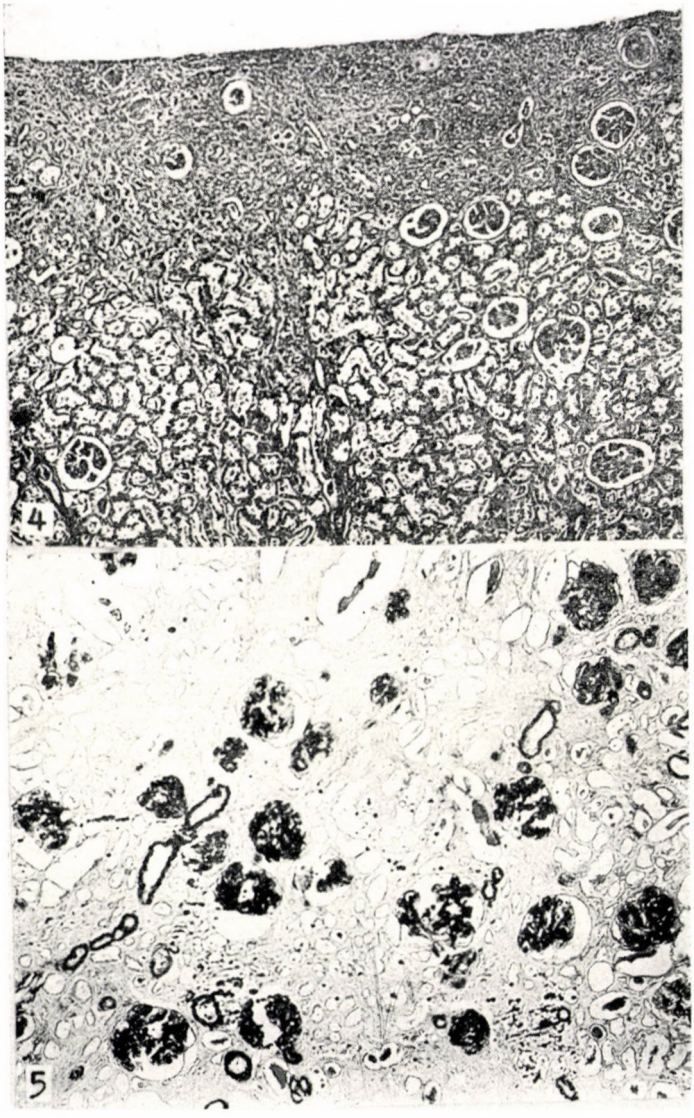


Fig. 4. Smooth part in the left kidney, with scarring of the subcapsular zone (Case 6)
Fig. 5. Renal section stained with gentian violet. Severe amyloidosis of the tufts in all the glomeruli is clearly visible (Case 10)

diffuse and marked lipoprotein infiltration was present and, to a considerably lesser extent fibrinoid degeneration. Since there were no haemorrhages, inflammatory reaction and destruction of vascular walls, the condition could not be identified with fibrinoid necrosis incident to nephrosclerosis ,in spite of the positive fibrin staining.

During life, the case was suggestive of malignant hypertension; *post mortem* diabetic glomerulosclerosis with very marked, mainly degenerative vascular changes were found. The case provided no clue to a connection between the two changes.

(x) J. K., a man 25 years of age, had had 11 years ago multiple osteomyelitis with fistulae for several years. Hypertensive complaints had been noted in the last two years. On admission, blood pressure was around 240/160 mm. mercury. In the ocular fundus, the papillae had undistinct contours, there was retinal oedema. The Congo test was negative. Albumin in the urine amounted to 0,6 g per 100 ml, serum NPN to 135 mg per 100 ml. Death ensued from uraemia.

The heart weighed 400 g, the kidneys 270 g. Histology disclosed moderate amyloid infiltration in the spleen, the liver and the adrenal glands. In the kidneys, amyloidosis was localized to the arteries, arterioles and especially to the glomeruli. No intact amyloid-free glomerulus occurred in any of the parts examined (Fig. 5).

During life, the eye symptoms, the extremely high diastolic pressure and the negative Congo test seemed to point to malignant hypertension. Autopsy revealed amyloidosis of the kidneys. The high blood pressure might have been due to the grave amyloidosis of the glomeruli.

III. Results

Analysis and evaluation

a) *Morphological changes in the arteries*

Our pathological investigations centred primarily around the kidneys. The technique used allowed differentiation between the following arteriolar changes.

(i) Circumscribed spots or rings in the intima of the vascular wall, staining with Sudan, taking a bright red colour with Azan, and a pale red with the MPH stain. The phenomenon is due to the passage of lipo-protein complexes into the vascular wall. This particular change is recorded in the literature under the terms of hyalinosis, hyaline necrosis, plasmorrhagia, fresh or primary hyalinosis. Since both our previous and present studies have shown the change to be characterized by the simultaneous presence of lipoid and protein, it is thought that the essence of the process is best characterized by the term lipoid hyalinosis (Fig. 6). Some authors take the red colour developed on staining with Azan for a sign of necrosis of the vascular wall. Our combined staining with Azan and MPH has, however, revealed that only part of the vascular and glomerular changes that become a brilliant red on Azan staining take the fibrin stain, so that this cannot be regarded as indicative of fibrinoid necrosis of the vascular wall.

(ii) Beside these acute phenomena, there were frequently found arteriolar changes which did not stain with Sudan, but became blue with Azan and a

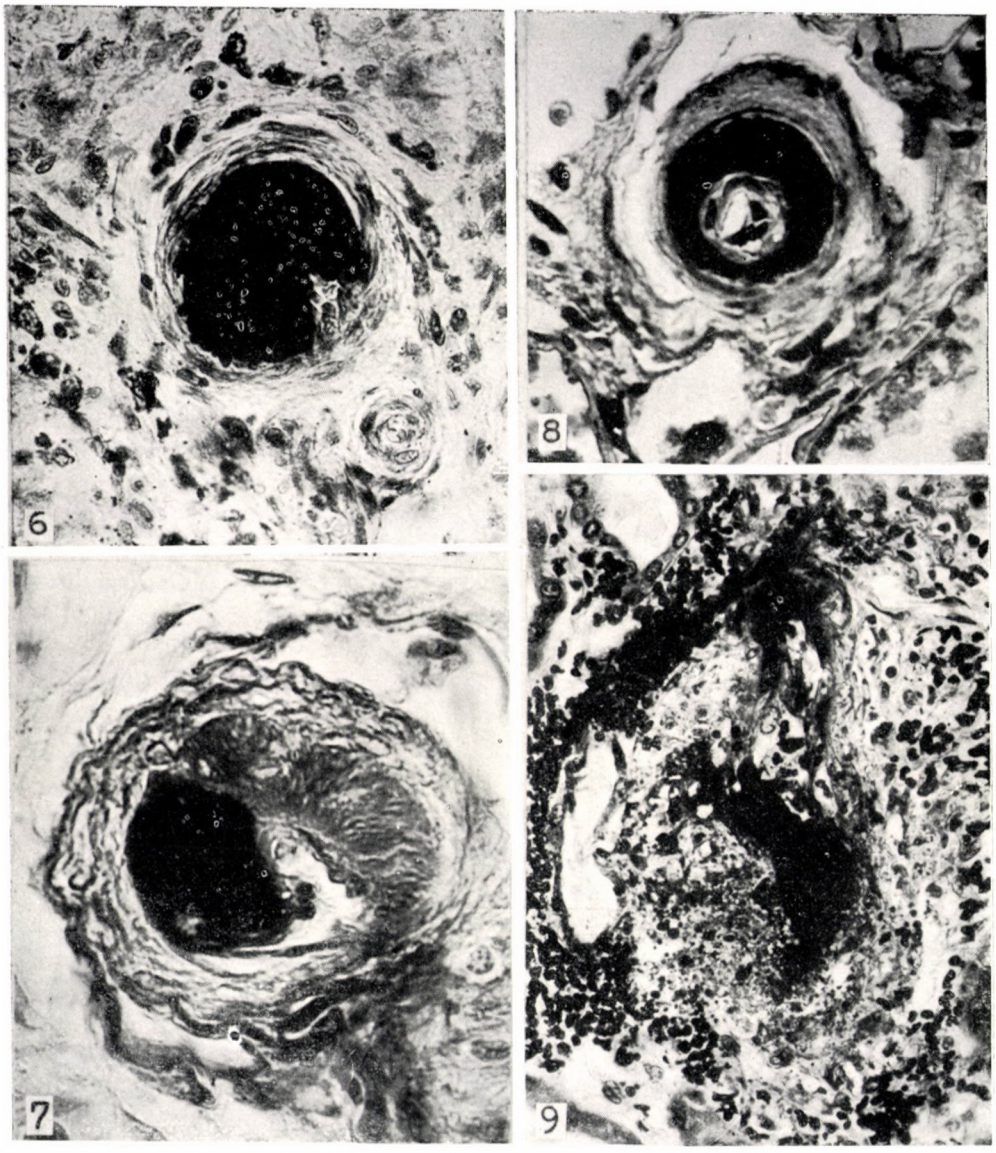


Fig. 6. High power view of an arteriole showing lipoid hyaline changes. Sudan stain. The flattened lumen appears in the lateral light sector

Fig. 7. High power view of an arteriole showing fresh and chronic changes. The dark spot corresponds to lipoid hyaline, the light-grey part of fibrous structure to collagenous hyaline Azan stain

Fig. 8. Subintimal fibrinoid-hyaline ring in an arteriole of the kidney which is of otherwise unaffected structure. Mallory's haematoxylin stain

Fig. 9. Necrotizing arteriolitis in the kidney. Total destruction of arteriole owing to fibrin deposition, haemorrhage and inflammation. Combined trichome stain

pale red with MPH. They mark a later stage of the above change, when lipoids have been absorbed and the protein takes a fibrous collagenized structure. The term hyaline generally covers this aspect. Silver impregnation discloses a fibrous structure, in contrast with the homogeneous structure of lipoid hyalinosis. Acute and chronic hyaline arteriolar changes may occur side by side in the different arteries, and even within the same vascular portion. Zakharievskaya's investigations have proved the periodically recurrent character of the process (Fig. 7).

(iii) A lipoid-poor or lipoid-free change, staining with Azan a bright red, with MPH a dark violet, is the so-called fibrinoid degeneration (fibrinoid necrosis), probably due to penetration of protein of coarser dispersity into the vascular wall (Fig. 8). It occurs in the arterioles in hypertension and in Kimmelstiel-Wilson's syndrome.

(iv) In its severest form, the change is marked by diapedesis of red blood corpuscles, a total destruction of the wall, often associated with thrombosis and the complete obliteration of the lumen (Fig. 9). Inflammatory signs and leucocytes in the walls of blood-vessels (necrotising arteriolitis) are often encountered. In protracted cases, periarteriolar granuloma may also develop.

It should be emphasized that we do not consider the changes described as distinctly separate categories ; they may occur in the arterioles side by side, as well as in succession.

While the benign form of nephrosclerosis is marked by lipoid hyalinosis and, at a later phase, by collagenized hyalinosis, the malignant variety is (in addition) attended by, in fact dominated by, fibrinoid necrosis, haemorrhage in the vascular wall and inflammatory infiltration. Productive endarteritis, i. e. the loose-structured, cell-rich and elastic free intimal proliferation in the small arteries is another salient feature (Fig. 10). In contrast with literary data, this represents an organisation process consequent upon the mucoid swelling of the subendothelial ground substance, rather than the healing of necrotic vascular walls. In working up our material we had relatively little opportunity to observe an unmixed pattern of mucoid-oedematous swelling of the subendothelial ground substance which is perhaps the earliest stage of the pathologically increased permeability (Fig. 11). The lamellar fibroelastosis of the arteries, whose pathogenesis and significance have been treated in detail by *Róna*, *Baló* and *Lábas* [28], occurs in both forms of hypertension, but is less marked in case of rapid progress. The degenerative change in the arterioles and pre-arterioles, a predominant factor in the causation of renal ischaemia at the advanced stage of the disease, shares a formost place with lamellar fibroelastosis in the range of vascular changes brought about by malignant hypertension. While arteriolar fibroelastosis only gives rise to a moderate stricture of the lumen and may be regarded as a reactive process of compensation, in consequence of lipoid hyalinosis the arteriolar lumen becomes tightly stenosed, often complete-

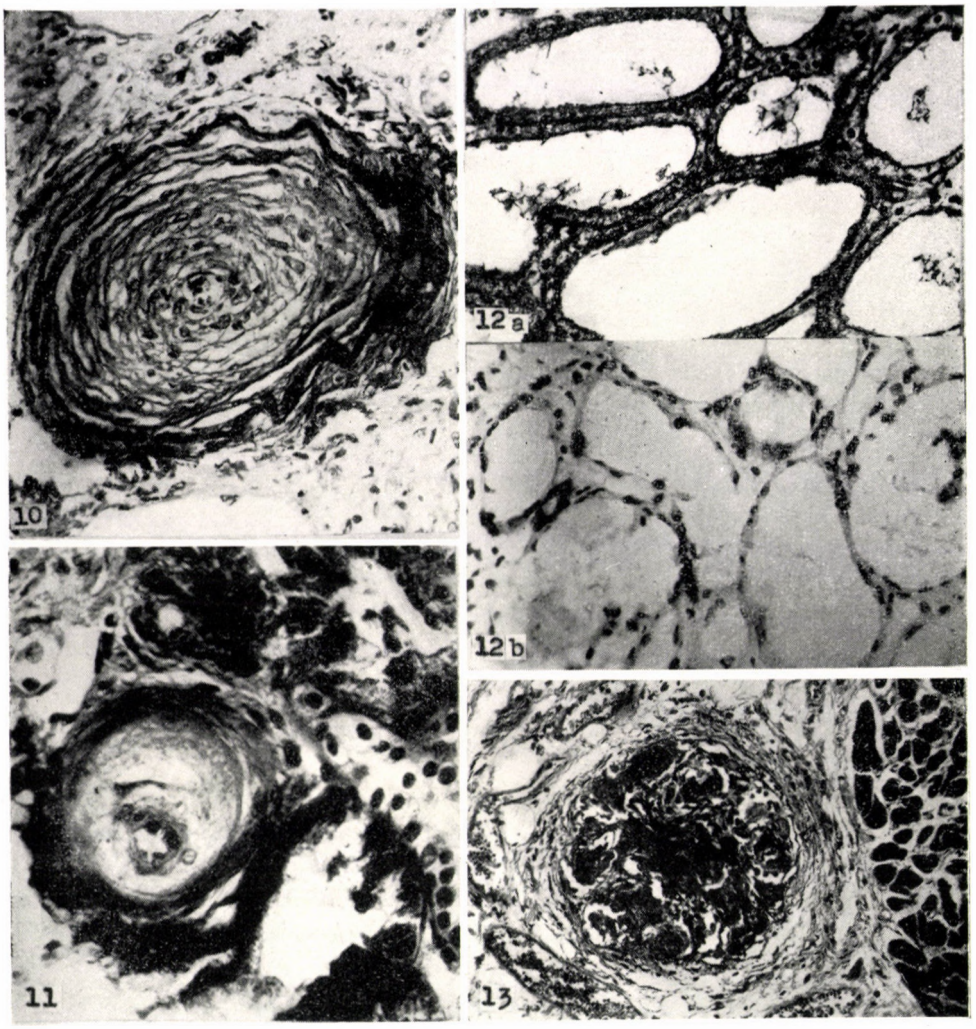


Fig. 10. Productive endarteritis, free of elastic elements, intimal proliferation, associated with extreme stenosis of the lumen. Van Gieson-elastic stain

Fig. 11. Extremely marked mucoid hyperplasia of the subintimal ground substance. Azan stain

Fig. 12. Alkaline phosphatase reaction in the kidney of Case 1 above hypertrophied tubuli, with maintained phosphatase activity. Below, atrophied, markedly distended phosphatase-negative tubuli

Fig. 13. Small coronary branch from the heart muscle, with fibrin thrombus in process of organization. Haematoxylin-eosin stain

ly obstructed. The difference in the morphological changes occurring in the single parts of the arterial system of hypertensive subjects is due to differences in function.

The underlying factor common to these arterial changes lies in the pathologically increased permeability of the membrane limiting the blood and the tissues. The factors primarily concerned in its origination include the protracted neurogenic spasm of the arterioles and a rise in intraarterial pressure, resulting in inadequate oxygen supply of the vascular wall and a consequential increase in the permeability of the subendothelial limiting membrane. The muscular hypertrophy of the prearteriolar and arteriolar walls and the ensuing degenerative changes in the smooth muscles likewise suggest prolonged spasm, which later gives place to infiltration of the subendothelial ground substance with lipoidprotein complexes originating from the blood-plasma. With the increase of permeability there eventually occurs a passage of corpuscular elements into the vascular wall and the process tends towards ultimate destruction of tissue. There is, however, every indication of a cooperation of permeability of the condition. Reference must be made to earlier investigations of *Rusznyák* and *Németh* [29], which have shown that the presence of lipoids greatly facilitates the passage of protein from the blood into the tissues. Our own findings *(Endes* and *Takács-Nagy)* have pointed to the same conclusion, demonstrating the simultaneous presence of both lipoid and protein to be the basis of the first phase of arteriolar changes. Also *Baker* and *Selikoff* [5] arrived at an identical conclusion. In our opinion, the process may be paralleled with *Anitchkov*'s [3] infiltration theory of the pathogenesis of atherosclerosis in larger arteries.

Hypertension is, at any rate in man, not the sole factor in the genesis of arteriolar necrosis. In man no rise in blood pressure ever develops at so speedy a rate and to such extreme a degree as in experimental hypertension. The decisive influence of the high diastolic pressure must go unchallenged ; it has indeed been invariably present in our cases of typical malignant hypertension associated with arteriolar necrosis. On the other hand, *we* have seen more than one case with a markedly high diastolic pressure of rather long standing in which necrosis of the blood vessels did not develop. *Fleming*'s [16] experiments furnish additional evidence against the exclusivity of high blood pressure as a causative factor. The toxic metabolites produced in uraemia may well tend to aggravate the increased permeability and precipitate necrosis of the arterioles ; we believe, however, that just the opposite is true, and that it is the loss of renal parenchyma brought about by rapid and complete obstruction of the arteries which provokes uraemia.

According to *Braun-Menendez* [7], uraemia and hypertension represent, with renal tissue destruction, three factors, two of which, if jointly present, lead to necrosis of the arterioles. Histologically, our cases of malignant neph-

rosclerosis were invariably found to be associated with both clinical and laboratory signs of renal insufficiency and uraemia. On the other hand, malignant hypertension and uraemia may be unattended by histological sings of malignant nephrosclerosis, as in our cases 3, 8 and 10. A factor of no less, if not still greater, significance in the production of arterial changes is the resistance of the vascular system, which is liable to be affected by exogenous influences, particularly by stress. This variation in the reactivity of the vascular system of particular organs, which is extremely susceptible to external influences, determines whether the sequelae of the injury due to hypertension appears in the coronary, the cerebral or the renal arteries. The present material has furnished further support to our earlier assumption that in certain cases of malignant nephrosclerosis arteriolar necrosis is brought about by a specific allergic arteritis (*Endes* and *Takács-Nagy* [14]).

Other renal elements reveal a full range of changes, from symptoms of atrophy consequent to inadequate blood supply to signs of fibrosis. The rate of progress seems to be inversely proportional to the number of scarred, hyaline glomeruli. When the progress is rapid, acute glomerular changes predominate, especially necrosis of the tufts or of the glomerulus as a whole, and haemorrhagic infiltration of the glomerulus, which may involve the connected tubules and the surrounding stroma. Signs of inflammation, such as intra- and extracapillary leucocytes, proliferation of the capsular epithelium, crescent formation, are common, especially in the malignant form. The tubular epithelium undergoes degenerative changes of varying character and degree, which *Lüders* [24], relying on an extensive material, has again attributed to increased permeability. The diminution, and even complete absence, of alkaline phosphatase activity observed in the tubules found by usual methods relatively unaffected, is indicative of a severe impairment of the subtler functions of the tubular epithelium. (Fig. 12). The increase in the amount of renal interstitium may vary in degree, the malignant form being attended with oedema, haemorrhages and inflammatory infiltration which is especially marked in hypertension complicated by an inflammatory factor. This acute, diffuse infiltration of leucocytic character is, however, *utterly different from the nodular lymphocytic one present in any hypertensive kidney as a sequel to parenchymal destruction*. It would, however, be erronous to combine, as has been attempted, *the reactive-inflammatory sings under the heading of pyelonephritis lenta* and, by generalizing them, lay undue stress on their pathogenic role [31*a*].

Other organs, such as the spleen, the pancreas, the suprarenal glands, the brain, the testicles and the intestinal wall, also show arterial and arteriolar changes. Broadly speaking, the damage is of a uniform type and, at any rate so far as our material is concerned, mostly less marked than in the renal arteries. Exceptions, however, are not infrequent, particularly in the spleen and in the pancreas whose small arteries may occasionally be found to exhibit severe

changes involving focal destruction of the parenchyma, — a prelude to the development of «patchy» organs conspicuous even to the naked eye. In the cases reported we met with two instances of «patchy» spleen and another two of focal necrosis in the pancreas. The small intramuscular branches of the cardiac coronary arteries showed changes differing from those in the renal arteries. While lipoid hyalinosis was but rarely encountered, endothelium-covered fibrin thrombi occurred in the lumen in 5 cases (Fig. 13). Thus, even after identical injury, the arteries of different organs show different morphological changes, possibly owing to the different functional demand on them. In 12 cases there were small necrotic foci in the wall of the hypertrophied left ventricle. They are unaccounted for by the arterial changes mentioned which are of far rarer occurrence and exclusively localized to the small branches. There is every reason to believe that the blood supply, reduced as it is through the sclerosis of the larger coronary branches, is unable to cope with the hypertrophied mass of ventricular musculature. This assumption has been substantiated by *Büchner* et al [9]. It should be stated at once that a preponderance of basophil cells in the anterior, or their invasion of the posterior lobe of the pituitary was, in agreement with the findings of *Berblinger* [6] and others, ascertainable in almost every case (in five and ten, respectively).

b) *The relation of malignant hypertension to malignant nephrosclerosis*

In 10 out of our 18 cases of malignant hypertension was there morphological evidence that in addition to hypertension other factors too are at work. They act either by turning an existing hypertensive condition malignant, or else by provoking malignant hypertension. On several occasions, the causal and temporal relation of hypertension to the adventitious factor was not definable with certainty. Four out of the ten mixed cases exhibited morphological signs of malignant nephrosclerosis, while the rest did not, death having been due to renal insufficiency brought about by the adventitious factor. It is interesting to note that, in seven of the cases, this factor consisted in a renal inflammatory process, while it was in three only that other causes, namely *developmental defect, amyloidosis or diabetes* were in play.

It is easy to see how an inflammation, itself a permeability increasing factor, aggravates by association with an existing hypertensive condition the already low resistance of the vascular walls. One half of our cases consisted either of a benign condition turned malignant, or of primary malignant hypertension, while in the other half the fatal syndrome was brought about by a pre-hypertensive, or associated, destructive renal factor. The renal factor, accordingly, seems to exert an overriding influence in the vitious circle of hypertensive disease.

It follows, then, that malignant hypertension is a clinical syndrome originating either from primary neurogenic hypertension or owing, in the light of the above evidence, part of its genesis to the agency of some, chiefly inflammatory, renal factor. This clinical conception is different from the morphologically well-defined category of malignant nephrosclerosis, which we continue to regard as indispensable in the purely morphological acceptation of the term. At the same time, however, we wish to uphold our interpretation of malignant nephrosclerosis as a terminal renal stage of hypertensive disease, opposite to *Fahr*'s view, — who had held that condition a primary nephropathy — in its own right.

The range of these investigations however is not confined to a merely theoretical significance ; they may, we believe, be credited with a definite practical value. There is no doubt that, in a notable percentage of hypertension cases, the underlying disease is some condition other than primary nephropathy as interpreted by *Fahr* [15]. This fact in itself bears out our view, for which there is, incidentally, the support of experience, that malignant hypertension constitutes a strong indication for thoracolumbar sympathectomy, provided no contraindication exists.

Although malignant hypertension of «nephropathic» origin is, for the most part, fairly easy to diagnose with a sufficient measure of exactitude, we have certainly come up against cases of this kind of hypertension that exhibited hardly any or absolutely no clinical difference from the primary malignant form of the condition. Hence our insistance that renal biopsy should invariably be performed when thoracolumbar sympathectomy is carried out a precaution that, in misindicated cases, will spare the patient at least the ordeal of an operation on the other side or further that sympathectomy on the other side may be combined with decapsulation.

Summary

(i) Renal biopsy performed concomitantly with thoracolumbar sympathectomy in cases of malignant hypertension has revealed no essential difference between renal tissue changes encountered in the early stage of clinically manifest malignant conditions and those seen in benign hypertension. The difference is a quantitative instead of a qualitative one. This allows the conclusion that, as regards its pathogenesis, malignant hypertension is identical with the benign form, the difference lying in the rapid progress of the former. *Fahr*'s description of the histology of the malignant variety is no doubt only characteristic of the terminal stage.

(ii) A scrutiny of our autopsies has lead to the conclusion that part of the hypertensive conditions clinically rating as malignant have some primary, mostly inflammatory, renal affection associated with them. Accordingly, malignant hypertension may develop either on identical lines with the benign form of hypertension, or alternatively from renal disease.

(iii) The underlying factor in vascular changes lies in the pathlogical increase in the permeability of the limiting membrane between blood and tissues. With the aggravation of dyshoria there is an increasing passage into the arterial wall of lipo-protein complexes, fibrin, blood and corpuscular elements, ultimately leading to its total destruction. There is no clinical proof of an exclusive role of the elevated blood pressure in the causation of arteriolar necrosis.

(iv) Malignant hypertension is a clinical syndrome covering both the rapidly progressing form of hypertension, termed malignant, and the malignant condition consequent upon nephropathies of varying origin. Malignant nephrosclerosis, characterized by necrotizing and inflammatory vascular changes, constitutes a morphological category, which may as such continue in use.

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О ПАТОГЕНЕЗЕ ЗЛОКАЧЕСТВЕННОЙ ГИПЕРТОНИИ

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1. Исследованиями посредством биопсии, проведенными при злокачественной гипертонии в связи с торако-люмбальным удалением симпатического нерва, было доказано, что при клинически несомненно злокачественных случаях гипертонии, в ранней стадии болезни, гистологические изменения почек, по существу, не отличаются от гистологических изменений, найденных на почках больных, страдающих доброкачественной гипертонией. Разница не качественная, а количественная. Это позволяет сделать то заключение, что патогенетически злокачественная гипертония, по существу, не отличается от доброкачественных форм, разница состоит скорее в быстром прогрессировании болезни. Описанная *Фаром* гистологическая картина, по всей вероятности, характерна лишь для последней фазы болезни.

2. Обработка казуистических случаев авторами доказывает, что в одной части случаев, кажущихся клинически злокачественной гипертонией, наблюдается первичное, а именно чаще всего воспалительное заболевание почек. Следовательно, одна часть злокачественной гипертонии возникает путем такого же патомеханизма, как и доброкачественная гипертония, однако, другая часть вызвана болезнью почек.

3. В основе изменений кровеносных сосудов лежит патологически повышенная проницаемость пограничной мембраны между кровью и тканями — dyshoria. По мере тяжести dyshoria, в стенку артерий проницают липо-протеиновые комплексы, фибрин, элементы крови и форменные элементы крови и этот процесс приводит в конечном результате к полному разрушению стенок артерий. На основе клинического материала нельзя доказать, что омертвение артериол является исключительно результатом повышения кровяного давления.

4. Злокачественная гипертония представляет собой клиническое понятие, синдром, заключающий в себе т. н. злокачественную форму болезни гипертонии с быстрой прогрессивностью, а также и злокачественную гипертонию, возникающую в связи с заболеваниями почек различного происхождения. Вызывающий омертвение и характеризованный воспалительными измениями артерий злокачественный нефросклероз представляет собой морфологическое понятие, применяемое и в дальнейшем в этом смысле.

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