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The Juxtaglomerular Apparatus in Malignant Hypertension of Man

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Summary. Investigation of the behaviour of the renal juxtaglomerular apparatus in 19 patients with malignant hypertension has shown that in kidneys fixed immediately after operation the juxtaglomerular granulation index is twice as high as in autopsy kidneys. The formation of renin by the epitheloid cells begins with the appearance of osmiophilic substances in the region of the endoplasmic reticulum. The first stages of granule formation are small rhomboid particles in the Golgi cisternes, which aggregate to form bigger round or polymorphic granules in the Golgi area.

In pathological conditions the substances synthesized may be set free and become active locally as a result of fibrinoid necrosis of the vascular wall. The rate of production is increased firstly by forcing rhe production of active agents in the preexistent epitheloid cells, secondly by transformation of the so-called bivalent cells and finally, by cell division.

In accelerated hypertension the production of renin also takes place in nephrons whose glomeruli, tubules and macula densa, are damaged. There is a correlation between blood pressure elevation and the juxtaglomerular granulation index.

Key words: Malignant hypertension – Juxtaglomerular apparatus – Renal renin production and secretion – Correlation between morphological renal changes, granulation index and blood pressure.

Zusammenfassung. Untersuchungen über das Verhalten des juxtaglomerulären Zellkomplexes der Niere bei 19 Patienten mit maligner Hypertonie haben folgendes ergeben: In operativ gewonnenen und sofort fixierten Nieren ist der juxtaglomeruläre Granulationsindex doppelt so hoch wie in Nieren aus dem Sektionsgut. Die Reninbildung der epitheloiden Zellen beginnt mit dem Auftreten osmiophiler Substanzen im Bereich des endoplasmatischen Reticulums. Kleine rhomboide Gebilde in Golgizisternen sind Vorstufen von reifen Sekretgranula, die sich im Golgifeld zu größeren runden oder vielgestaltigen Sekrettropfen zusammenlagern.

Unter pathologischen Bedingungen können infolge fibrinoider Gefäßwandnekrosen Sekretsubstanzen lokal frei und lokal wirksam werden. Vermehrte Arbeitsleistung erfolgt zunächst durch Forcierung der Sekretproduktion in den präexistenten epitheloiden Zellen, sodann durch Transformierung sogenannter bivalenter Zellen und schließlich durch Zellneubildungen.

Reninproduktion findet bei akzelerierter Hypertonie auch in solchen Nephronen statt, deren Glomerula und Tubuli samt Macula densa strukturell geschädigt sind. Es besteht eine Korrelation zwischen Höhe des Blutdruckes und Höhe des Granulationsindex.

Introduction

The structure and function of the juxtaglomerular apparatus of the kidney have been of almost constant scientific interest during the last 50 years (Cain and Kraus, 1969; Meyer, 1972). Numerous reports indicate that the production of renin occurs at a site where preglomerular intravascular pressure and volume, and electrolyte concentrations in the upper part of the distal tubule are able to influence its release (Tobian, 1960–1967; Endes et al., 1963; Reeves, 1965; Thurau and Schnermann, 1965; Leyssac, 1967; Vander, 1967; Eigler, 1967).

We report here our observations concerning the human juxtaglomerular apparatus in malignant hypertension, from which we were able to deduce new cellular and pathogenetic information. The questions we tried to answer were the following:

1. Is there a difference in granulation index values in material fixed immediately after nephrectomy and autopsy material?
2. How are specific (renin) granules formed and how is the product secreted?
3. By what means do the juxtaglomerular cells increase their rate of secretion?
4. Is there a difference in distribution of the granulated juxtaglomerular apparatus in different zones of the renal cortex?
5. Are there any correlations between morphological changes in the kidneys, the level of granulation index, and the height of blood pressure?

Material and Methods

The kidneys of 24 men were examined. 5 of them served as controls, having been removed by nephrectomy. The details of these normotensive, normonatriemic patients are shown in Table 1.

In 9 men and 2 women (21–53 years) with malignant hypertension and terminal uremia bilateral nephrectomy was performed. In table the details of blood pressure levels, duration of hypertension etc. are shown. Plasma renin levels were mostly high but sometimes still within the limits of normal. Post-operatively blood pressure levels tended to fall (see Table 2).

8 additional observations of accelerated hypertension come from our autopsy material. In these cases, preparation and fixation of the tissue was carried out between 8 and 20 h after death. The age range of these 7 men and 1 woman was from 39 to 73 years. This group was more heterogenous with regard to the etiology and the duration of their hypertension (or the malignant phase) and in the degree of renal insufficiency than the operative group. 3 patients died from a hypertensive cerebral haemorrhage, the others from cardiac and renal insufficiency or from pulmonary embolism (Table 3).

Table 1. Normotonic, normonatraemic patients without pathological findings of the kidney-parenchyma

Current no. biopsy no. age (years), sex	Clinical diagnosis	Juxtaglomerular granulation index (JGI)
1) 1358/76 27, ♂	Embryonal carcinoma, right testis. Semicastratio, lymphadenectomy. Right nephrectomy	16,66
2) 1909/76 68, ♂	Tubular adenoma, partly oncocytic, of the right kidney	11,65
3) 2768/76 65, ♀	Renal tubular carcinoma, inferior pole of the right kidney	12,64
4) 2770/76 65, ♀	Renal tubular carcinoma, inferior pole of the right kidney	10,90
5) 4982/76 28, ♀	Diverticulum of a renal calyx	10,00

Histology

Thin slices of the renal cortex and adjacent parts of the renal medulla were fixed in 5% formalin and partly in Helly's solution. Fat staining was carried out, and after conventional processing to paraffin wax sections were stained with Hematoxylin-Eosin, Elastic van Gieson, Goldner, PAS, the Prussian blue reaction, and the fibrin stain of Weigert.

Electron Microscopy

Small tissue cubes of nephrectomy material were fixed in glutaraldehyde, post-fixed with OsO_4 and embedded in Epon. Silver impregnation of semithin sections was done by the method of Movat. In addition sections were stained with methylene blue, basic fuchsin and toluidine blue. Contrasting of ultrathin sections was carried out with uranyl acetate and lead citrate. Sections were studied with EM Philips 300.

Granulation Index

After extensive preliminary experiments we applied the special stains of Bowie (1935/36) and a Trichrome-Masson stain in the modification of Endes et al. (1969). The result of these procedures are shown in Figures 1 a and b, which show the importance of performing the techniques carefully, notably in the differentiation stage.

The determination of the granulation index in Bowie-stained section preparations was carried out by the method of Hartroft and Hartroft (1953). In every case, at least 500 glomeruli were recorded.

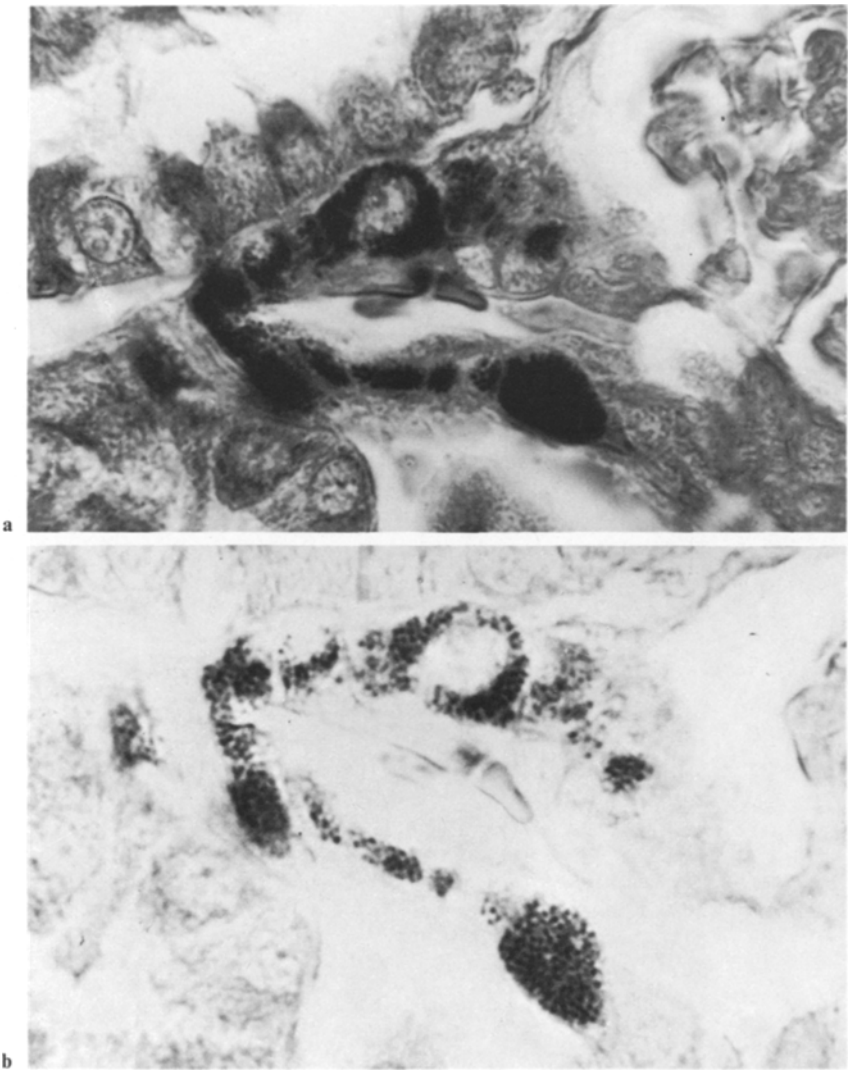


Fig. 1. Two different results of Bowie-staining in the same juxtaglomerular apparatus. In the upper picture (intensive staining) single granules are not clearly separated, while they are easily delineated in the picture beneath. Magnification × 1400

Results

1. Controls

In these 5 patients two kidneys (case 1 and 5) were normal in all parts, of the 3 remaining organs only the tumor free pole was examined. Histologically

Table 2. Malignant hypertension, nephrectomy material

Current no. biopsy no. age (years), sex	Clinical diagnosis	Duration a) hypertension (years) b) malignant phase (months)	Blood pressure (mm Hg) a) before b) immediately c) 3–4 months after nephrectomy	Period (months) of hemodialysis before nephrectomy	Histology	JGI
6) 12616/71 44, ♂	Malignant hypertension; death by hemorrhagic shock	2 6	250/180 —	1	arterio-arteriolosclerosis and hyalinosis; fibrinoid arteriolonecrosis of focal or sector-like type	99
7) 12674/71 41, ♂	Malignant hypertension	2	240/140 160/100 normotensive	6	high-grade-concentric stenosing arterio-arteriolosclerosis and glomerulosclerosis	116
8) 13018/71 48, ♂	Accelerated hypertension	— 8–9	250/150 170/105 normotensive	4	concentric stenosing arterio-arteriolosclerosis and glomerulosclerosis; fibrinoid swelling of vascular wall	155
9) 13152/71 27, ♂	New attack of a proliferative glomerulonephritis; accelerated hypertension	1 3–4	230/150 170/105	4	high-grade concentric arterio-arteriolosclerosis	129
10) 4542/72 21, ♀	Accelerated hypertension; previous eclampsia; microangiopathic hemolytic anemia	4 5	220/130 160/100 normotensive	4	glomerulonephritis (90–95 g); marked sclerosis, hyalinosis and sporadic fibrinoid necrosis of renal arteries and arterioles	105
11) 5703/72 41, ♀	Malignant hypertension; chronic glomerulonephritis with cirrhosis	? 6	220/100 140/100 normotensive	4	hyalinisation of nearly all glomeruli; high-grade concentric arterio-arteriolosclerosis (45–50 g)	37
12) 9858/72 42, ♂	Malignant hypertension	6 ?	210/130 190/95 160/85	10	stenosing and obliterative concentric arterio-arteriolosclerosis (76–85 g)	34,2
13) 14220/74 35, ♂	Malignant hypertension; acute glomerulonephritis	? 8	280/180 160/100 120/70	3	membranoproliferative glomerulonephritis; marked fibrosis and stenosis of arterial and arteriolar walls, in parts recently necrotised subendothelial layer	80
14) 15413/74 27, ♂	Chronic glomerulonephritis; malignant hypertension and anemia	10 ?	220/110 160/80 —	3	high-grade stenosing and fibrosing alterations of the vascular walls, some serum insudations (45–60 g)	31
15) 4540/75 25, ♂	Sclerosing glomerulonephritis; malignant hypertension; renal anemia	4 ?	210/110 160/90 160/70	7	most glomeruli hyalinised; stenosing, onion-like fibrosis of the vascular walls of medium-sized and small arteries; hyalinisation of the vasa afferentia; serum insudations, fibrinoid necrosis (70–80 g)	40,2
16) 5460/75 53, ♂	Malignant hypertension; glomerulonephritic cirrhosis	7 > 1	270/140 160/100 died	7	most glomeruli hyalinised concentric fibrosis of the vascular walls; serum insudations (65–70 g)	82,5

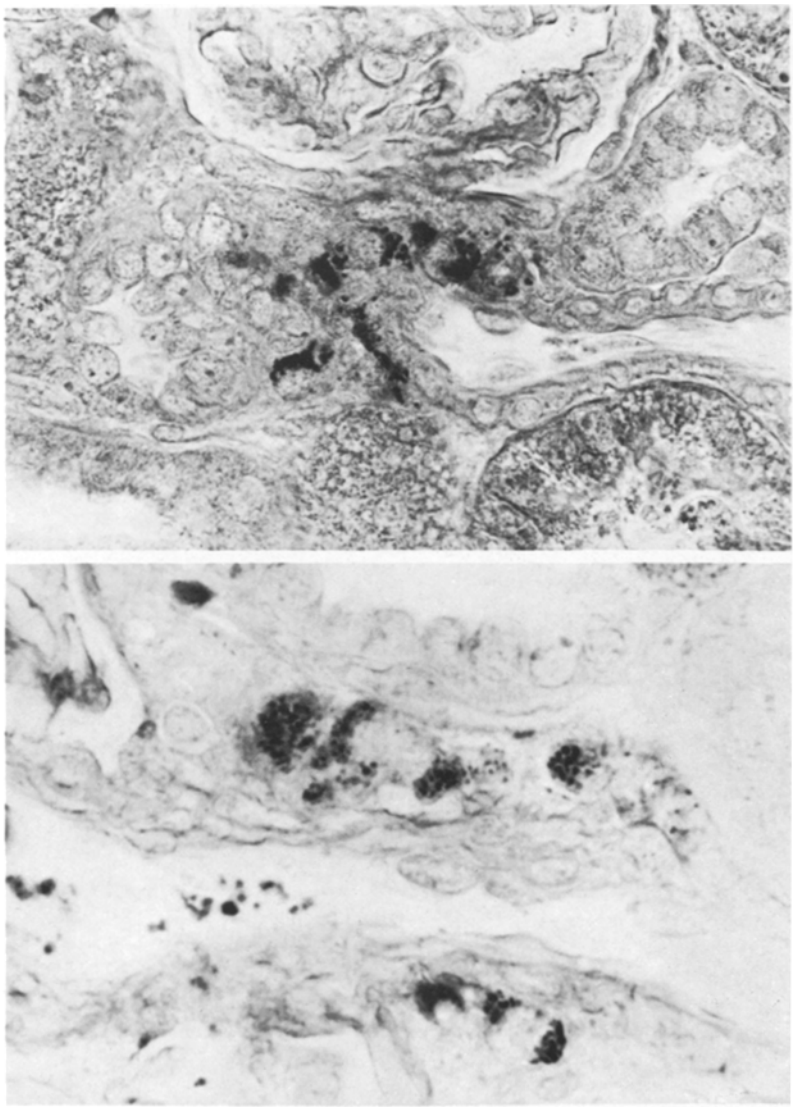
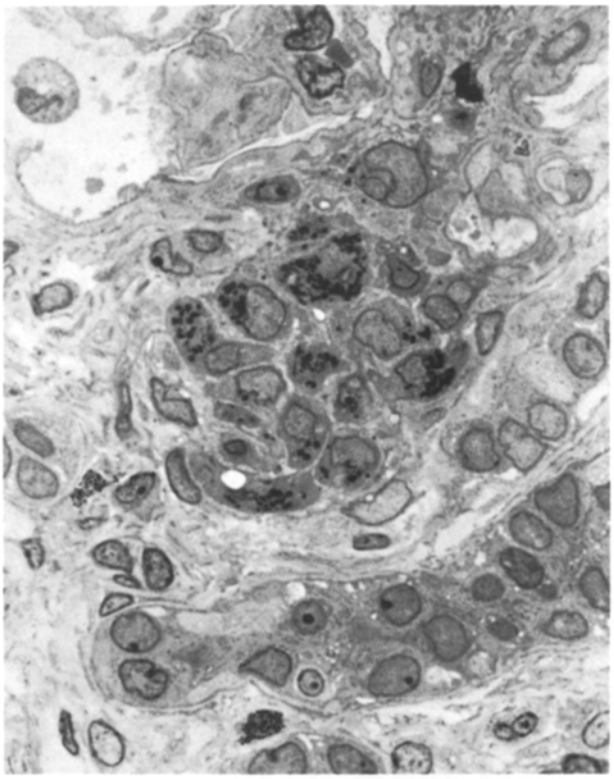


Fig. 2. Two juxtaglomerular cell-complexes in malignant hypertension with an unusually strong granulation (+ + + + according to Hartroft). Bowie. Magnification × 1400

Fig. 3. Malignant hypertension: cross-section of a vas afferens rich in highly granulated cells. Glomerular stalk in the upper half, beneath the macula densa. Two mast cells with small round granules nearby. Semithin-section. Toluidinblue. Magnification × 1200

Fig. 4. High secretory activity in some epitheloid cells of a vas afferens. Different width of the rough endoplasmatic reticulum, well-developed Golgi body, lots of round, ovoid and polymorphous granules besides triangular and rhomboid secretory substances. Original magnification 1 : 2800



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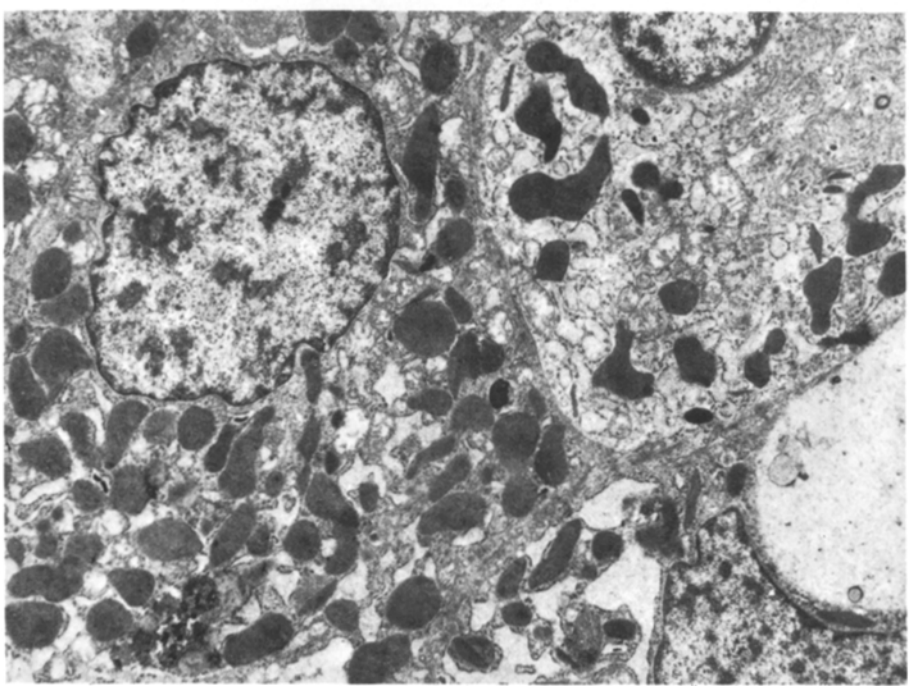

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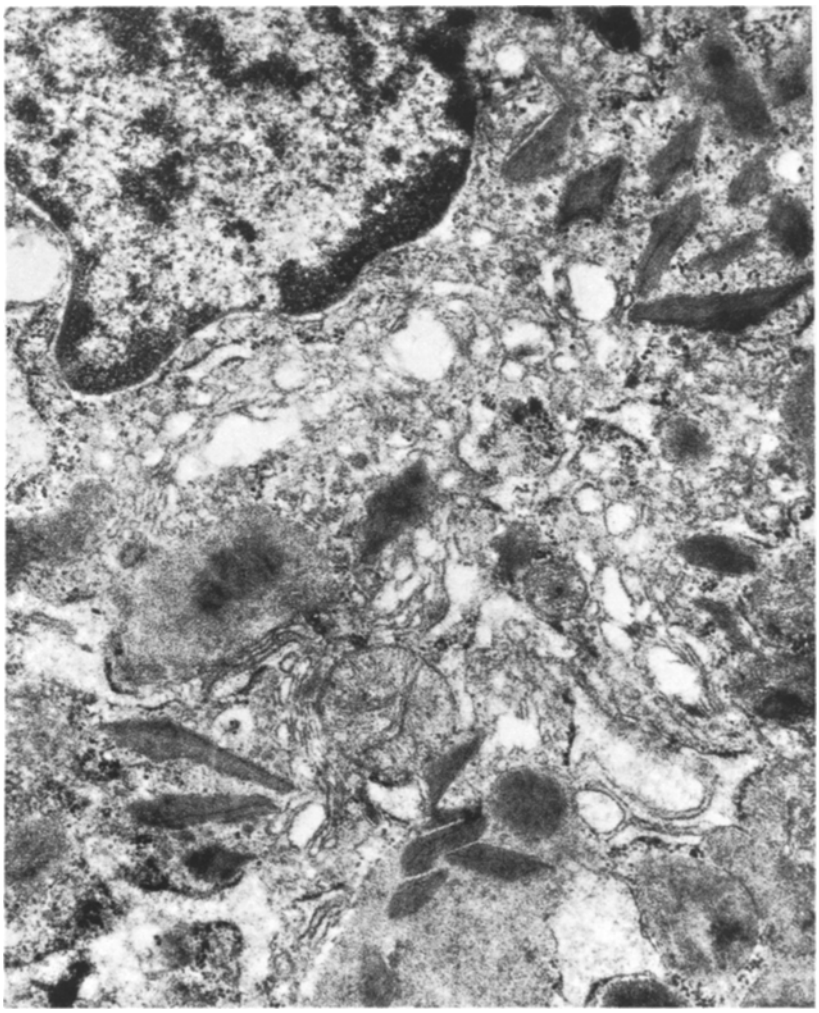

Fig. 5. In this granulated epitheloid cell the widened endoplasmic reticulum, the well-developed Golgi body and numerous rhomboid granules indicate an intense de-novo-synthesis of secretory material. Original magnification 1:9000

there is no abnormality. The epithelia of the macula densa are normal in number, cell and nucleus size, and ultra-structure. The juxtaglomerular granulation index is 12.4 on average, with a range of 10–16.66.

2. Malignant Hypertension, Nephrectomy Material (Table 2)

The kidneys removed were more or less shrunken. Histological examination reveals extensive scarring of cortex and medulla. The walls of arteriae interlo-

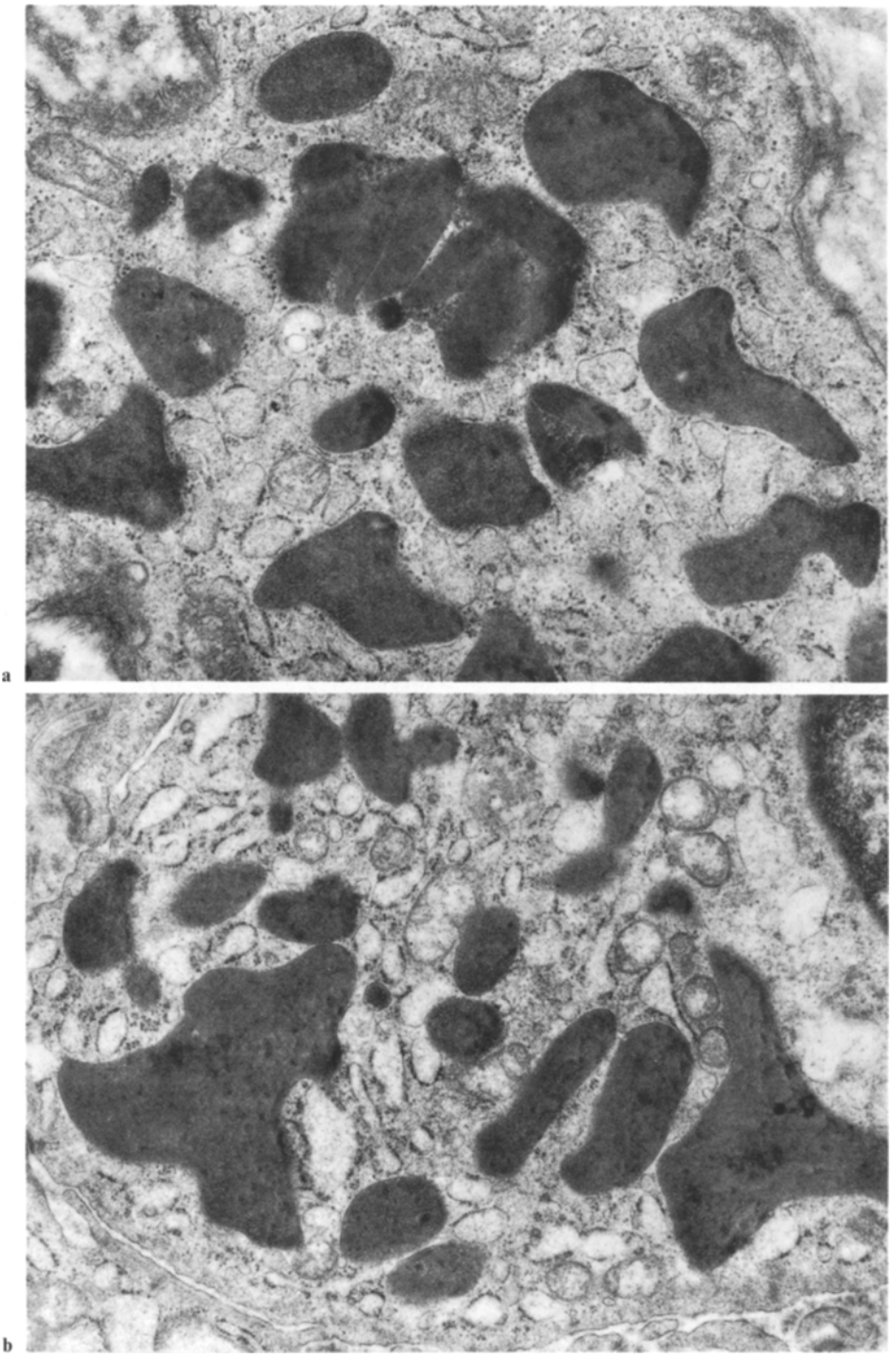

Fig. 6. With increasing formation of secretion the epitheloid cells of the vasa afferentia still contain in part rhomboid figures lying together (upper picture), but the big polymorphous forms of confluent granules predominate. Original magnification 1:9000

Table 3. Malignant hypertension, autopsy material

Current no. autopsy no. age (years), sex	Clinical diagnosis	Duration of a) hypertension b) malignant phase	Blood pressure (mm Hg)	Histology	JGI
17) 526/69 50, ♀	Malignant nephrosclerosis	16 years 1 year	270/150	concentric sclerosis of small and medium-sized arteries; fibrinoid necrosis of arterioles and glomerular capillaries	42
18) 528/69 61, ♂	Malignant nephrosclerosis Fahr; cerebral haemorrhage	? 5 weeks	240/140	onion-like sclerosis of the walls of medium-sized and small arteries; hyalinosis of the arterioles; fibrinoid necrosis	58
19) 66/70 73, ♂	General angiosclerosis; pulmonary embolism	? 2 years	240/160	concentric sclerosis of small and medium-sized arteries and of arterioles; hyalinisation of glomeruli (80–90 g)	29
20) 177/70 60, ♂	Malignant hypertension; cerebral haemorrhage	10 years ?	300/150	arterio-arteriolosclerosis without necrosis; solitary hyalinisation of glomeruli	41
21) 220/70 62, ♂	Malignant hypertension; cerebral haemorrhage	15 years 1 year	250/140	concentric onion-like sclerosis of the walls of medium-sized and small arteries; hyalinisation of the arterioles (90–90 g)	43
22) 126/74 39, ♂	Malignant hypertension; pneumonia; uremia	5 years	270/80	concentric arteriosclerosis; hyalinosis of the arterioles; fibrinoid necrosis	36,6
23) 135/75 47, ♂	Malignant hypertension; uremia; encephalomalacia	12 years	220/120	onion-like connective tissue hyperplasia of arteries; partly hyalinosis, partly serum insudation and fibrinoid necrosis	38,9
24) 89/76 53, ♂	Malignant hypertension; encephalopathy; pneumonia	8 years 6 years	240/150	hyalinosis of arteries and arterioles; hyaline thrombi in the vasa afferentia and glomeruli; intimal oedema and fibrinoid necrosis	41,26

bares, arcuatae and corticales radiatae show a massive concentric and onion-like sclerosis or a less dense, obliterative fibrosis of the intima. The vasa afferentia are narrowed or even completely obliterated by hyaline change in their walls either segmentally or throughout. Disturbances in permeability have led to oedema of the intima and to so-called fibrinoid necroses of the vascular wall. Such necrosis is not seen in vasa efferentia. In other regions glomeruli and tubules are better preserved, but hyaline thrombi are seen in glomerular capillaries and in arterioles. But there are also nephrons with a good preservation of their structures. In all parts of the cortex, there is a striking multiplication

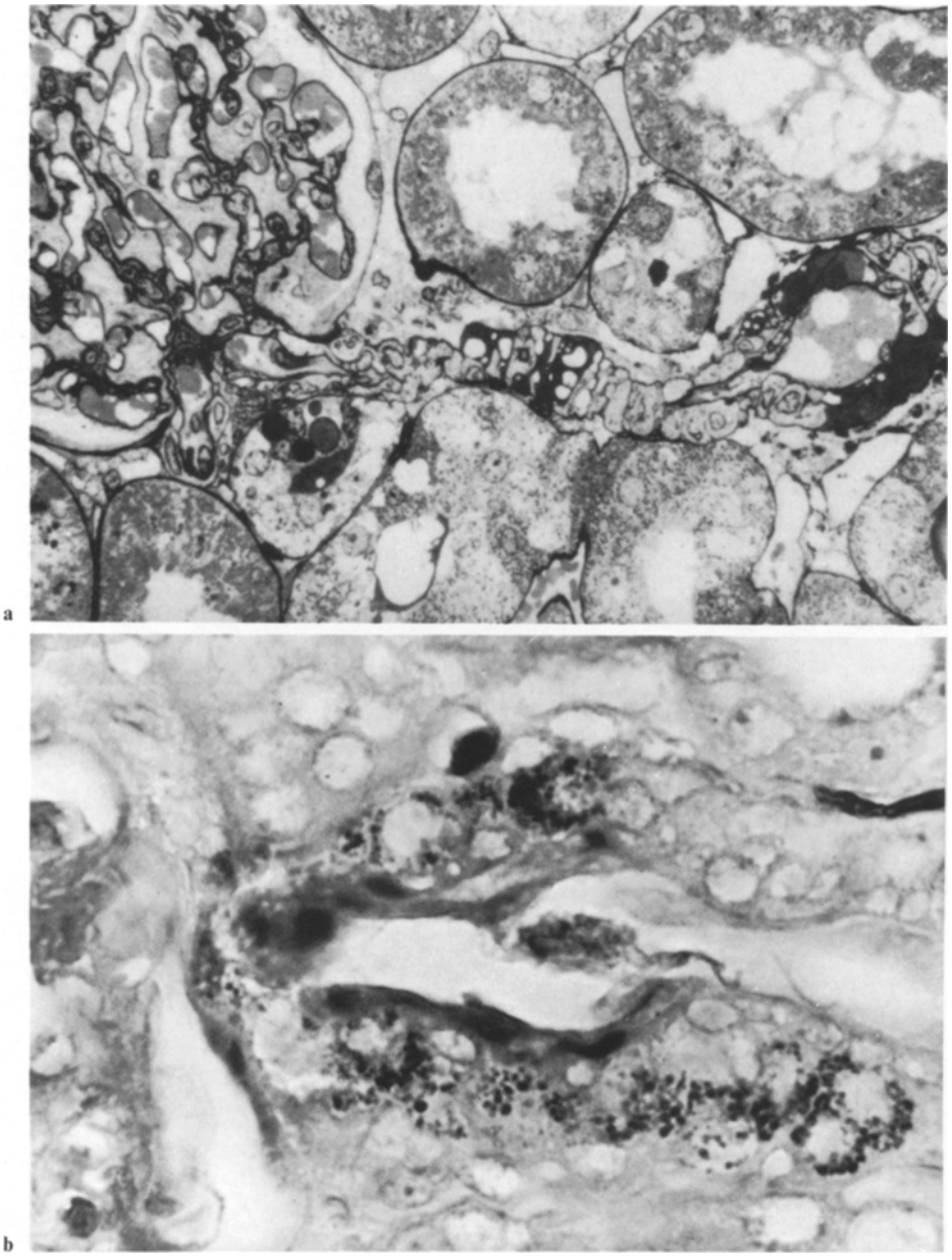

Fig. 7. a Oblique section of a vas afferens with focal fibrinoid necrosis of the wall. Semithin-section. Movat. Magnification ×800. **b** Fibrinoid necrosis of the intima and wall of a richly granulated vas afferens. In such necrosis renin substances may be set free and become effective locally. Bowie. Magnification ×1400

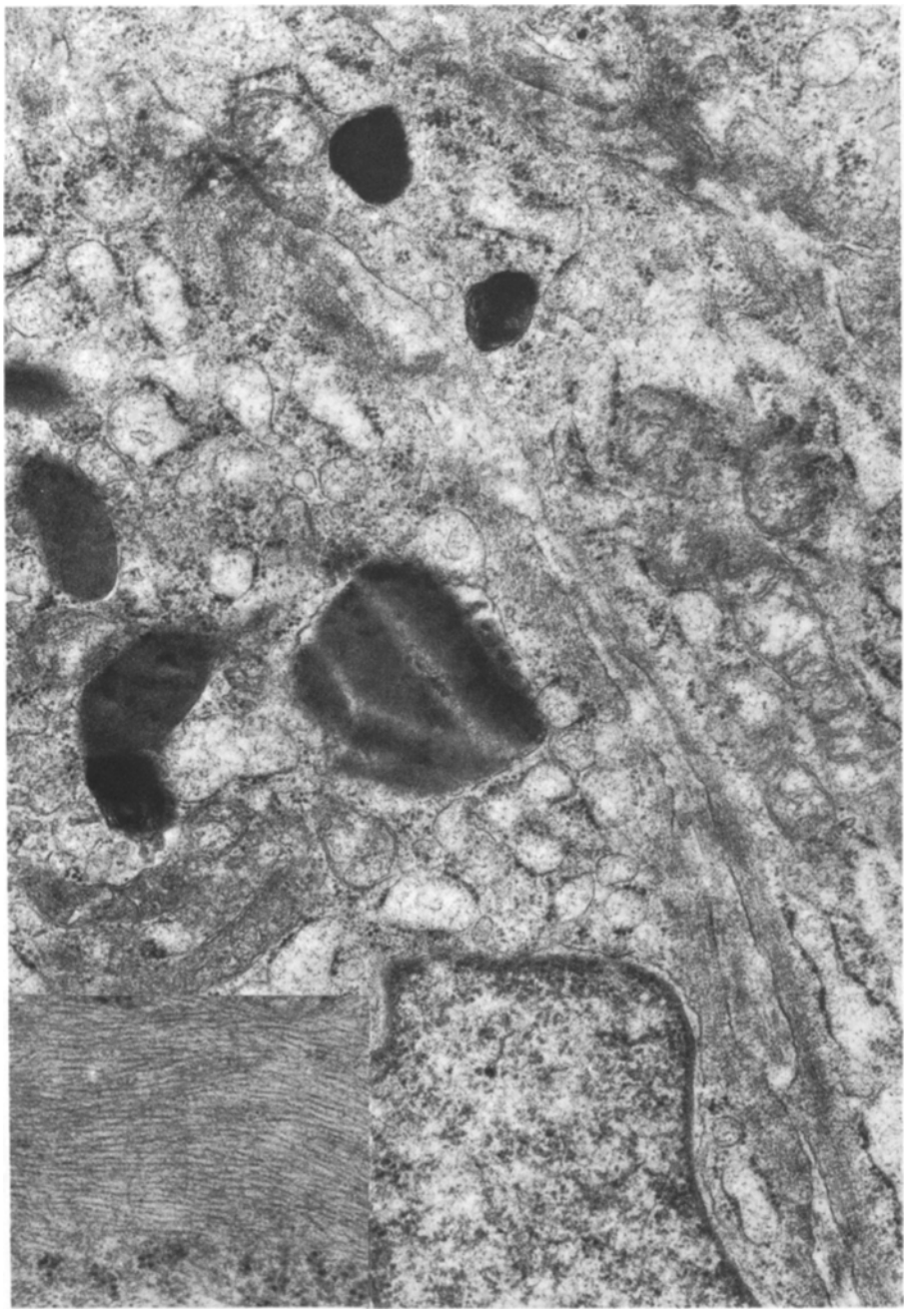

Fig. 8. Specific granules (partly rhomboid) and myofilaments in two vascular wall cells. Filaments mainly near the cell membran, cut in length and breadth. Magnification ×27,500. Inset at the bottom left. Magnification ×45,000

and swelling of cells in those vascular segments of the juxtaglomerular apparatus which are free of hyalinisation. Almost every intact vas afferens contains numerous secretion granules identified by the Bowie-stain. Granulated epitheloid cells are often found even in the vasa afferentia of partially or almost completely hyalinised glomeruli. The granulated epitheloid cells can also be seen in the juxtamedullary zone. The average juxtaglomerular granulation index of 83 (range 31–155) is raised to many times the normal value (Figs. 2 and 3). Electron microscopy shows the large epitheloid cells of the vasa afferentia to surround the vascular wall in several layers. The nuclei are large and round, with a loose chromatin network and a prominent peripheral nucleolus unlike the nuclei of smooth muscle cells. Their cytoplasm is completely expanded, thus their cell membrane is smooth and not crenated as in smooth muscle cells. The pale cytoplasm contains (apart from numerous free ribosomes) abundant rough endoplasmic reticulum widening into bays bordered with ribosomes. Many large Golgi bodies are found, usually near the nucleus. Their cisternes are ample. The bags of the Golgi apparatus frequently include small triangular or rhomboid, sharply outlined osmiophilic particles with honeycombed, hexagonal sub-structures, corresponding to early forms of secretion granules (Figs. 4 and 5). As they grow bigger, they fill the Golgi bags as roundish granules. Ultimately, they are found in large numbers all over the cytoplasm. A number of mature, homogenous secretion granules may aggregate and flow together to form chains of granules with waist-like incisions (Fig. 6). During maximal secretory activity, the epitheloid cells are crowded with secretion granules in the large spaces of the endoplasmic reticulum, whereas the other cytoplasmic organelles are reduced in number.

The epithelial cells of the macula densa never show hypertrophy or hyperplasia, are often flattened and appear atypical. Some of the epithelial basement membranes are intensively hyalinised, the intertubular interstitium is often sclerosed and sometimes contains loose round-celled infiltrations.

The ultra-structural findings in these patients indicate greatly increased renin production in the afferent arterioles. This is suggested by intensive formation of cytoplasmic structures involved in secretion synthesis, and in particular by the appearance of secretion granules in variable stages of maturation.

3. Malignant Hypertension, Autopsy Material (Table 3)

The histological changes are similar to or identical with those of our second group. Stenosing wall lesions of variable degree are present in small and medium-sized arteries, and resemble a productive endarteritis with scarring. In the arterioles, hyaline thrombi, an acute oedema of the intima or fibrinoid wall necroses are detectable in most of the cases (Fig. 7). The average juxtaglomerular granulation index of 41 (range 29–58) is clearly elevated when compared with normal values.

Discussion

Our methods of study have been shown to be suitable for the assessment of structural and functional changes in the epitheloid cells of the renin producing

apparatus (see also Pfob, 1970). We have previously shown (Cain and Kraus, 1971) that there is a relationship between the granulation index determined by the method of Hartroft and Hartroft (1953) and the renin content of epitheloid cells, which account for 90% of the total renin in the JGA (Faarup, 1968).

As the investigations were done partly in kidneys from our autopsy material and partly in surgical material the effects of autolytic changes must be considered. In a comparison of surgically removed and autopsy kidneys the granulation index was found to be on average, twice as high in surgical as in autopsy kidneys. These finding suggest a quantitative influence of autolysis on the demonstrability of renin granules 8–20 h after death.

An increase in the granulation index in hypertensive kidney when compared with the normal can be diagnosed in autopsy material during the first 20 h post mortem, but in these cases we should be cautious when specifying the coefficient of increase.

The kidneys of patients suffering from malignant hypertension are most appropriate for studies of the method of production of specialised secretions in the JGA since they have very high granulation indices and plasma renin levels; a permanently increased de-novo-formation of granules might be expected in these patients. Our results and those of Fisher (1966), Fisher et al. (1966), Lee et al. (1966), Gomba et al. (1970) suggest the juxtaglomerular secretion granules are lysosomal particles; their exceptional position is based on the fact that they contain a specific protease, namely renin.

Renin secretion is an active, energy consuming phenomenon. Electron microscopy shows condensing osmiophilic particles of varying sizes, single or in groups, next to circumscribed accumulations of ribosomes and glycogen, in particular in the little bags of the Golgi system. Some of these exhibit streaky or honeycombed, hexagonal sub-structures. The formation of these hexagons can be explained by the arrangement of phosphatide molecules around water droplets by the action of their hydrophilic groups, as demonstrated by Stockenius (1962). Within Golgi cisternes we often find small rhomboid particles, which we regard as the precursors of mature secretion granules. They gradually aggregate, conglomerate and finally form large, roundish, oval or polymorphus secretion droplets with homogenous osmiophilia. These droplets may fuse, forming chains of granules with waist-like incisions. Some granules show aggregations of ribosomes on their surface. The earliest product of secretion, especially the sharply outlined rhomboid particles, are smaller than mitochondria whilst mature granules are larger. The vigorous secretory cell activity is documented by remarkably large Golgi complexes, rich with inclusions, by a very abundant, spacious ergastoplasm, by an augmentation of free ribosomes and by a swollen nucleus with loose chromatin network and a prominent, mostly peripheral nucleolus. All these criteria indicate that the high granulation index observed is caused by an intensified synthetic activity and not by storage of specific granules because of a defect in the excretory mechanisms. Our present findings suggest that the formation of the granule substance starts within the endoplasmic reticulum; the maturation of the granules is accomplished in the Golgi apparatus, and the storage takes place in the free cytoplasm.

At present there are no positive data about the exact mechanism of the release of secretion from the cells. We cannot be certain whether the product is excreted into the arteriolar lumen or into the intercellular space surrounding the vessel. Serum insudations and fibrinoid swelling of the walls of vasa afferentia suggest there may be an alternative mechanism of excretion under pathological conditions. If simple oedema of the intima is able to alter the physiological extra- and intracellular environment, this effect will be much stronger where there are severe vessel wall lesions with necrosis of granulated epitheloid cells: lysosomal mechanisms will be put into operation and will effect the release of the contents of granules; these may have a local effect.

Our third question is: what method is used by the epitheloid cells to increase enzyme production? A high rate of synthesis is suggested by an increase of the ergastoplasmic reticulum, by widespread Golgi complexes, by a multiplication of free ribosomes, by an enlargement of the nucleus and the nucleolus, and by a rising granulation index of the preexisting epitheloid cells. But there are other methods of augmenting enzyme synthesis.

Cain and Kraus (1971) found in the preglomerular part of the vas afferens of rabbit kidneys a population of bivalent cells with a character intermediate between smooth muscle cells and epitheloid cells. These may be activated to become either muscular or predominantly secretory. We consider that these cells exist in man. When required their internal cell structure becomes transformed: cytoplasmic organelles for the synthesis and formation of granules are built up and kept ready, whereas myofilaments decrease in number and are pushed to the cell periphery by the increasing number of other organelles (Fig. 8).

Compensatory hyperplasia may also occur as shown by the striking cell multiplication in malignant hypertension. Although we found no mitotic figures in our section preparations, the great increase in number of juxtaglomerular cells in malignant hypertension can be interpreted only as a consequence of cell division. Our third question may thus be answered as follows: there are several steps in increasing granule output, at first an enhanced activity of preexisting epitheloid cells followed by an activation and transformation of so-called bivalent cells and finally proliferation of cells capable of secretion. Goormaghtigh-cells are also involved in this process.

Our fourth question concerns the distribution pattern of granulated cell complexes in different zones of the cortex. In control kidneys, granulated juxtaglomerular apparatuses are mainly present in the peripheral cortex, whereas the juxtamedullary parts of the cortex contain only sporadic granulated epitheloid cells. This pattern seems to be the rule in human kidneys after cessation of normal growth. This is in agreement with the observations of Cain and Kraus (1971) on the behaviour of the juxtaglomerular apparatus in brown Wistar rats during growth, maturation and senescence. In the kidneys of men suffering from malignant hypertension we saw a striking hypertrophy, hyperplasia and hypergranulation of the juxtaglomerular complex in the juxtamedullary zones with many granulated cells corresponding to degrees III and IV in Hartrofts's scale. Thus there is not only an increased granulation of the normal renin producing vascular poles but in addition a reactivation of renin production in cortical areas, normally active for only a short time during maturation and

growth of the kidney. We may conclude from these findings that in pathological states juxtaglomerular cells of the adult JGA can once again become secretory.

Our fifth question was, are there correlations between the morphological changes in the kidneys, the level of granulation index and the height of blood pressure?

Structural preservation is necessary for function. In malignant hypertension there are usually large areas of glomerular, periglomerular, vascular and tubular scarring together with partial or sector-like alterations of glomerular capillaries and of afferent arterioles. However areas of juxtaglomerular activity persist. The arterial lesions consist partly of hyalinisation of the vessel wall with stenosis, partly of a recent oedema of the intima and partly of focal fibrinoid necroses of the wall. It is likely that a causal relationship exists between the intravascular coagulation and necroses of smooth muscle cells and granulated epitheloid cells – single or in groups – within the section of vessel affected. It is remarkable that these wall lesions chiefly affect the vas afferens, whereas the vas efferens is usually normal. In some kidneys, histological examination suggested that a collateral circulation is developing by the formation of glomerular shunts, which might improve the local supply of blood. The pathophysiological consequences of these morphological changes will be as follows (Cain and Kraus, 1969): if the *receptor* mechanism of the juxtaglomerular apparatus is eliminated, *information* can no longer be obtained by this specialised tissue; if the site of *production* of secretion is affected, there can be no response to a stimulus to synthesis; if the structure of the *reacting organ* is damaged the renin-angiotensin-aldosteron-mechanism will not be effective. Correlations exist between the particular type and localisation of the morphological alteration on the one hand and the renin secretion in the JGA, on the other. Close correlations between the blood pressure values and the granulation index are evident in our observations.

There are, however, some findings which cannot be interpreted easily: sometimes we see ultra-structural indications of an intensified formation of secretion in vasa afferentia whose glomeruli are almost or completely obliterated. The lack of any congruity between the behaviour of the juxtaglomerular granulation index and the epithelial cells of the macula densa (we often find a high granulation index of the epitheloid cells with total atrophy of the macula densa) argues against the necessity for chemo-reception via the macula densa for stimulation of renin production as postulated by Thurau (1960–1971) in accelerated hypertension. This statement is in agreement with findings of Gomba et al. (1970) which illustrate formation of renin granules in auto-implanted kidney tissue without activity of macula-glucose-6-phosphate-dehydrogenase.

In a former study (Cain et al., 1972) we pointed out that renin production is not merely a problem of cellular morphology, because cells are not independant individuals. The interactions of various cells in a tissue or organ impose controls which are of necessity closely integrated and which may therefore be readily disturbed by injury. In accelerated hypertension renal changes of this kind may be accompanied by undefined extra-renal stimuli causing excess renin production.

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