Anatomy. — *Occurrence of mitotic divisions in glomeruli in the kidney of pregnancy.* By PH. H. HARTZ. (Curaçao N.W.I.)

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Although it has been known since many years that the significant lesions of "the kidney of pregnancy", i.e. eclampsia and prae eclampsia, are to be found in the glomeruli, there still exists much difference of opinion with respect to their morphology and nature. TH. FAHR (as quoted by BELL (1) and MASTBOOM (2)) found that in eclampsia the glomeruli were enlarged and ischaemic. The walls of the capillaries were swollen, the cellborders were ill-defined and sometimes the nuclei seemingly had disappeared. Only exceptionally was an increase of endothelial nuclei observed, which FAHR attributed to an associated infection. FAHR considered the lesions as degenerative and for this reason used the term glomerulonephrosis as designation. It should be noted that FAHR did not use modern methods for the staining of the basement membranes of the glomerular capillaries.

BAIRD and SHAW-DUNN (3) and KELLAR, ARNOTT and MATHEW (4), using the azocarmine-aniline blue stain, found in eclampsia and prae eclampsia ischaemia and a moderate enlargement of the glomeruli, swelling of the endothelial cells and sometimes an increase of endothelial nuclei. There was also swelling and sometimes fibrillation of the capillary basement membranes. The authors considered the lesions as inflammatory. BELL (1, 5) using the same technic, found in fatal cases of eclampsia a marked narrowing of the glomerular capillaries, caused usually by an increase in thickness of the capillary basement membranes but sometimes by a increase of endothelial cells. Some increase of endothelial cells was found in many cases and occasionally this increase was rather striking but never pronounced enough to warrant a diagnosis of acute glomerulonephritis. Originally BELL (1) was inclined to consider the increase of endothelial cells as an inflammatory phenomen, that is, a form of glomerulonephritis. He also stressed its frequent occurrence. Later on he changed his opinion and stressed the degenerative nature of the glomerular lesions (5).

Recently MC. MANUS (6) investigated the glomerular lesions in 16 cases of eclampsia with his periodic acid-Schiff's reagent technic (7, 8) and came to conclusions which are fundamentally different. In contrast with the authors cited before he did not find thickening of the basement membranes of the glomerular capillaries or proliferation of the endothelial cells but constant swelling and vacuolation of the cells of the mesangium

or axial spaces (9, 10) which sometimes also involved the endothelial cells. Mc. MANUS considers this vacuolation or "reticulation" as the specific lesion of the glomerulus in eclampsia.

It follows from this short review of the literature that one of the disputed points is whether proliferation-especially of the endothelial cells-really does occur in the glomeruli of the kidney of pregnancy. Proliferation on a restricted scale can only be proved with certainty by the finding of mitotic divisions in the cells concerned and for this the material of the authors cited was unsuited since it was obtained from routine autopsies and, as BAIRD and SHAW DUNN (3) and KELLAR and associates (4) specially mention, already showed autolysis. As I had already been able to demonstrate mitoses in glomeruli in glomerulonephritis, malignant sclerosis and septicaemia (11) and later in cases of pyelonephritis, pneumonia and subacute bacterial endocarditis (12) in all of which autopsy had been performed within 45 minutes after death, it was deemed worth while to search for mitoses in the glomeruli of the kidney of pregnancy in such cases in which renal tissue could be obtained under the same favorable circumstances.

Material and Methods.

In case No. 1 autopsy was performed 30 minutes after death, in cases Nos. 2, 3 and 4 not more than 5 minutes after death. Blocks of renal tissue, not more than 3 mm thick, were cut for fixation. In case No. 1 the Bouin-sublimate mixture was used as fixative; in the other cases the tissues were fixed in Stieve's fluid, which in cases Nos. 2 and 4 was modified by replacing the glacial acetic acid by a 2 per cent aequous solution of trichloracetic acid (13). The blocks of tissue were embedded in paraffin by Péterfi's methylbenzoate-celloidin method and the sections stained with the periodic acid-Schiff's reagent technic, with Masson's tetrachrome, with the azan stain and with orcein.

Case 1.

A coloured woman, 32 years old, multigravida, was admitted in the hospital with the classic symptoms of eclampsia and died after a few hours. As the patient had only very recently immigrated from one of the British West Indian islands and moreover was not married, no anamnestic data were available.

Gross notes. The liver weighed 2000 grams and showed the haemorrhagic necroses typical for eclampsia and an enormous subcapsular haematoma. The kidneys weighed 300 gram; in the cortex there were numerous small cysts, on the cut surface the markings were normal. The heart weighed 385 gram; there were many subendothelial haemorrhages in the left ventricule, especially in the ventricular septum. The uterus contained a dead, almost full term child.

Microscopic examination of the kidneys.

The glomeruli varied in size; sometimes they appeared to be smaller than normal so that the capsular space was fairly wide. Other glomeruli were somewhat enlarged. The epithelial cells were distinct. The capillary basement membranes were very little thickened. The axial spaces were very distinct and the cells contained in them were conspicuous and sometimes vacuolated. The capillaries contained very little blood; occasionally there were a few leukocytes. In many glomeruli there was an increase of endothelial cells in several but not all of the loops.

In a few glomeruli mitoses were found. All stages of the mitotic division were represented; centrioles and achromatic spindles were very distinct. In some instances they ocurred probably in the cells of the axial spaces, but others could with certainty be localized inside the capillaries. No mitoses were found in the epithelial cells. The lumina of the proximal convoluted tubules were wide and contained a little precipitate. Their epithelium was somewhat swollen and sometimes contained small vacuoles. Necrosis or hyaline droplet degeneration were completely absent. A few loops of Henle and distal convoluted tubuli contained hyaline casts.

The small cortical arteries and arterioles were normal; only in the larger arteries a slight thickening of the intima was found.

Case 2.

A coloured woman, 32 years old and primigravida, was admitted into the hospital with typical eclampsia and died 18 hours after the onset of the symptoms. One week before being admitted her urine had been examined and was found to be normal.

Gross notes. The liver weighed 1600 gm and showed the typical haemorrhagic necroses. The kidneys weighed 327 gm, their color was brown with a few greyish spots. On section the markings were not distinct. The pyelum of the right kidney was slightly distended. The heart weighed 250 gm and did not show anything abnormal.

The uterus contained a dead child the size of which corresponded with the ninth month of pregnancy.

Microscopic examination of the kidneys.

Only part of the glomeruli were moderately enlarged but many showed an increased cellularity. The epithelial cells could easily be recognized by their localization and their typical nuclei. The basement membranes of the glomerular capillaries were thin; the axial spaces were broadened and contained very conspicuous, sometimes large and finely vacuolated cells. The capillaries contained very little blood; in many loops the endothelial cells were swollen and in some places seemed to block the lumen. The protoplasm of these swollen epithelial cells was often vacuolated. In still other places isolated glomerular loops were blocked by

swollen endothelial cells and by very thin fibers which stained red with the periodic acid-Schiff's reagent technic. In a few glomeruli mitoses were found. They occurred in the cells of the axial spaces and in the endothelium. No mitoses were found in the glomerular epithelium.

The lumina of the proximal convoluted tubules were wide; they contained only little precipitate. Their epithelium was of normal height; in many cells the rods were distinct, in others they were replaced by small oxyphilic granules arranged in rows. In the distal convoluted tubules and in the collecting tubules there were acidophilic casts and large accumulations of a strongly acidophilic granular precipitate. Sometimes a cast in a distal convoluted tubule was covered by flattened epithelial cells. In many collecting tubules containing casts or precipitate there was patchy necrosis and desquamation of the epithelium.

The smaller cortical arteries and the arterioles were normal. A few larger arteries showed some thickening of the intima.

Case 3.

A coloured woman, 17 years old and primigravida, mens. IX entered the hospital with the typical symptoms of eclampsia and died after a few hours. No anamnestic or clinical data were available. At autopsy haemorrhagic necroses were found in the liver.

Microscopic examination of the kidneys.

Part of the glomeruli were moderately enlarged and there was sometimes a definitely increased cellularity. The epithelial cells were larger than normal; and sometimes contained small hyaline droplets. The basement membranes of the capillaries appeared as thin, sometimes wrinkled lines. The axial spaces contained large connective tissue cells with finely vacuolated protoplasm. The capillaries contained very little blood, many loops were plugged by swollen endothelial cells also with vacuolated protoplasm. In other loops the endothelial cells were smaller but the lumina were compressed by the broadened axial spaces. Sometimes the peripheral part of a loop consisted of an inextricable mass of cells and very thin fibers.

Mitoses were found in both the cells of the axial spaces and in the endothelium. Sometimes 2 mitoses were observed in the section of one glomerulus.

There was some slight swelling of the epithelium of the proximal convoluted tubules. The bloodvessels did not show pathologic changes.

Case 4.

A coloured woman, 36 years old and VII gravida, entered the hospital because of albuminuria and gross edema of the legs. At the end of every previous pregnancy she had suffered from albuminuria, hypertension and edema but had always completely recovered after delivery. On admission the blood pressure was 230/140. One day after admission she became comatose and died suddenly.

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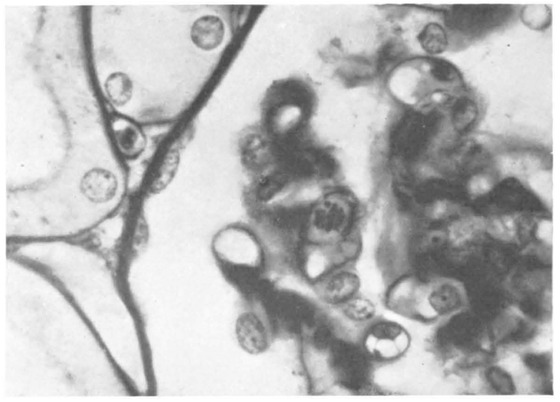

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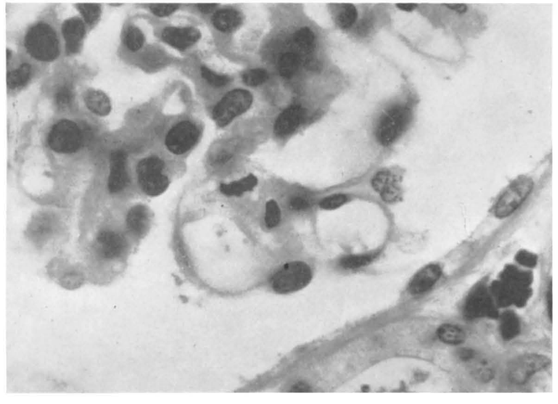

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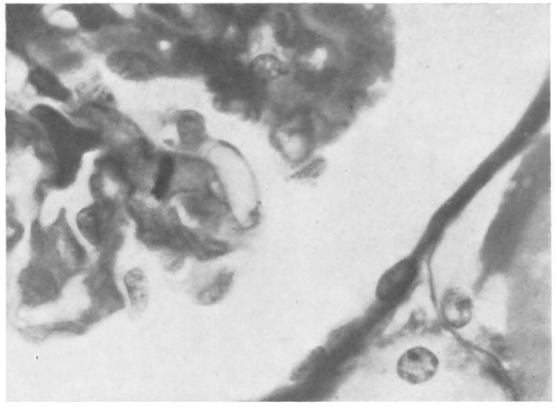

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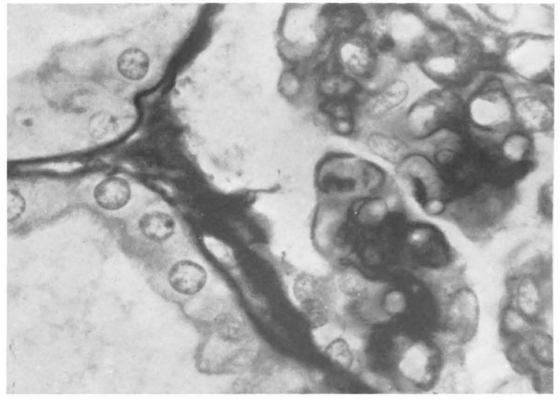

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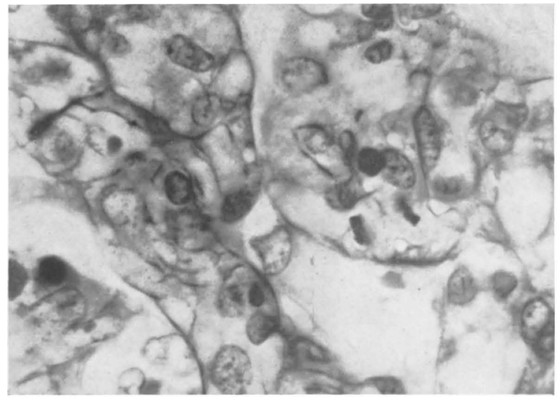

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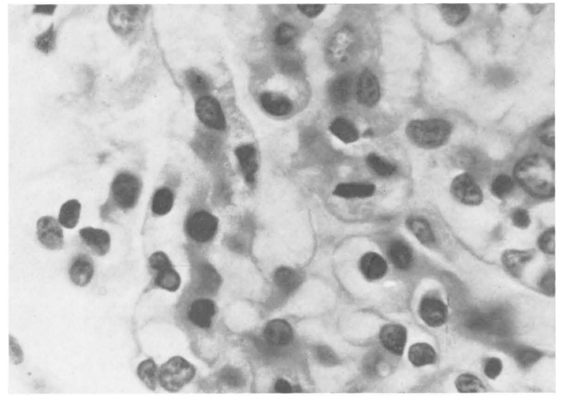

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PHOTOMICROGRAPHS.

1. Case 1. Mitosis in endothelial cell.
   Periodic acid-Schiff's reagent technic.
2. Case 1. Mitosis in cell in axial space.
   Masson's tetrachrome with Fastgreen F. C. F.
3. Case 2. Mitosis in cell in axial space.
   Periodic acid-Schiff's reagent technic.
4. Case 3. Mitosis in endothelial cell.
   Periodic acid-Schiff's reagent technic.
5. Case 4. Mitosis in endothelial cell. There is some fibrillation of the basement membrane.
   Periodic acid-Schiff's reagent technic.
6. Case 4. Mitosis in cell in the axial space.
   Masson's tetrachrome with Fast Green F. C. F.
7. Case 3. Swollen and finely vacuolated endothelial cell.
   Periodic acid-Schiff's reagent technic.

Gross notes. The kidneys weighed 422 gm, the cortex was swollen and pale. The pyelum of the right kidney was slightly distended. The liver weighed 1940 gm and did not show necroses or haemorrhages. The heart was hypertrophic and weighed 404 gm.

A living, almost full term child, which died shortly afterwards, was removed from the uterus at the beginning of the autopsy.

Microscopic examination of the kidneys.

The majority of the glomeruli were enlarged; there was also increased glomerular cellularity. The glomeruli contained very little blood and an occasional glomerulus appeared to be solid. A few epithelial cells showed hyaline droplet degeneration. There was some "reticulation" of the axial spaces. The capillary basement membranes were thin; the number of endothelial cells of many loops was definitely increased and many endothelial cells were swollen. There were very few glomeruli which showed some shrinking combined with a thickening of the capillary basement membranes.

Mitoses in the glomeruli were found fairly easily in the endothelium as well in the cells of the axial spaces; sometimes 2 mitoses were observed in the section of one glomerulus. They were found in all stages. The tubuli were wide and contained a little granular precipitate. There was no degeneration of the tubular epithelium. A few mitoses were observed in the epithelium of the proximal convoluted tubuli.

Hyaline degeneration of the arterioles was completely absent; in the larger arteries there was sometimes a slight thickening of the intima and occasionally a duplication of the inner elastic membrane.

Discussion.

In the first 3 cases the diagnosis "eclampsia" was obvious; in case no. 2 there existed probably haemoglobinuria and microscopically lesions usually present in "lower nephron nephrosis", but here on a restricted scale, were found in addition to the glomerular lesions; a combination which is not infrequent in eclampsia (14). In case no. 4 the clinical diagnosis was praeeclampsia; the fact that apart from slight changes in the larger arteries and a few shrunken glomeruli the renal lesions were identical with those found in the other 3 cases and that, apart from the hypertrophic heart no other pathologic changes were found at autopsy, makes the diagnosis reasonably certain.

From the microscopic examination several facts emerge. In accordance with the findings of BELL (1, 5) and of BAIRD and SHAW DUNN (3) the tubuli showed very little pathologic changes. It is therefore very probable that the severe degenerative lesions observed by FAHR were, in so far as he was not dealing with cases of beginning cortical necrosis, caused by autolysis.

The changes observed in the glomeruli consisted of the vacuolation of the axial spaces, first described by MC. MANUS, occasional fibrillation of the capillary basement membranes, swelling of the endothelial cells and the presence of mitotic divisions in both the cells of the axial spaces and in the endothelial cells. Thickening of the capillary basement membranes, when present, was discrete. There were no mitoses in the glomerular epithelial cells.

The finding of mitotic divisions in glomeruli in the kidney of pregnancy has never been reported before. Since mitoses are irrefutable proof of proliferation the significance of proliferation in glomeruli has to be considered. A review of modern textbooks and monographs (5, 15, 16, 17, 18, 19) shows that proliferative manifestations are considered the most important and prominent feature of inflammation of the glomerulus in clinical acute glomerulonephritis and in the subclinical glomerulonephritis often found in various infections. The proliferation of the endothelial cells is the most striking, but according to MC. MANUS some of the additional cells are to be found in the axial spaces (6). Other manifestations of the inflammatory reaction in clinical acute glomerulonephritis consist of swelling of the endothelial and sometimes of the glomerular epithelial cells, of discrete thickening of the capillary basement membranes with, in later stages, the formation of intracapillary fibers, whereas exsudation may be quite inconspicuous or almost completely absent. Epithelial crescents are only found in combination with haemorrhages (18). In our cases all these features, even the formation of intracapillary fibers in an isolated capillary loop, were present, though less strikingly so than in clinical glomerulonephritis. It is therefore tempting to consider the glomerular changes in the kidney of pregnancy as inflammatory. Against this conception two objections can be advanced: 1. the constant presence of vacuolation of the axial spaces in the kidney of pregnancy, which so far has not been found in glomerulonephritis and 2. that in my cases there was glomerulonephritis as complication, a suggestion already made by FAHR. Against the first objection it can be argued that, as the inflammatory reactions in glomerulonephritis and in eclampsia and praeeclampsia are probably due to different causative factors, morphologic differences are to be expected as happens also in inflammation caused by different infective agents. That nephritis, which in Curacao is very rare, should in the absence of infectious processes complicate every one of the reported cases is so improbable, that further discussion is superfluous.

The conception of the glomerular lesions in the kidney of pregnancy as inflammatory in nature is certainly not new, but is rendered much more probable by the proof that proliferation really occurs. There is certainly no reason for describing the glomerular lesions as purely degenerative and since, as has already been mentioned, the tubuli show very little pathologic changes, FAHR's term "glomerulonephrosis", which still figures in several textbooks, should be discarded.

Summary.

In four cases of the "kidney of pregnancy" in which autopsy could be performed in very favorable circumstances for the subsequent microscopic examination, mitotic divisions were found in the glomeruli. They occurred in the endothelial cells of the capillaries and in the cells of the axial spaces. Since endothelial proliferation in glomeruli is considered the most important feature of glomerular inflammation and other lesions, usually found in glomerulitis, were also present, it is suggested that the glomerular lesions of the kidney of pregnancy are inflammatory in nature.

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