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Vascular and Circulatory Changes in Renal Cortex in the Anuric Crush-Syndrome.

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In this communication, the vascular and circulatory changes in the renal cortex (tissues fixed in formol; preparations stained by Masson's trichrome method) of 4 cases of fatal, so-called renal crush-syndrome[1] are briefly reported. In each of the 4 cases, the subjects had received crushing injuries of the extremities and died 4 to 9 days later following the development of marked oliguria and anuria.

Histologic examination of the kidneys disclosed the following state of the microscopic circulatory structures:

(1) glomerular ischemia or oligaemia.

(2) in some zones, slight congestion of the inter-tubular capillaries with inter-tubular oedema.

(3) (a) enlargement of the afibrillar constituents of the juxta-glomerular apparatus[2,3] and very marked granularity of its cells; eventually degeneration of these cells. (b) increase in number and hypertrophy of the afibrillar (granular and non-granular) cells of the media of the pre-glomerular, and, exceptionally, the interlobular arterioles.

(4) occasionally (in 2 of the 4 cases) the presence of Siegmund's intimal granulomas[4] and parietal fibrinoid thrombi in the interlobular veins.

A more detailed account follows:

Glomerular changes: the erythrocytes in the loops are either absent or scanty; the mesangium (Zimmermann[5]), is unaltered; the loops are filled with coagulated plasma and a few enlarged endothelial cells. The wall of the distended infundibulum sometimes contains an increased number of spindle-shaped cells separated by fine collagen fibrils. The glomerular space is distended by coagulated (by fixation) albuminous material.

The cellular layer of Bowman's capsule is unaltered, but as the result of the distension of the glomerular space, the hypertrophied epithelium of the neck of the proximal convoluted tubule appears incorporated in the glomerular capsule.

An incidental finding in one case is fat embolism of the tufts of slight degree.

The inter-tubular capillaries: the blood circulation between the tubules has been maintained apparently by the collateral circulation of the renal capsule and Ludwig's arterioles, since the inter-tubular capillaries contain erythrocytes; in some places they appear slightly engorged. Inter-tubular oedema is conspicuous except in the cortex corticis. It is accompanied by slight histiocytic reaction and an early deposit of collagenous fibrils.

The juxta-glomerular apparatus: normally, the afibrillar cells of the renal arterioles in man are devoid of granules,[2,6] however, they are abundant in the anuric kidneys associated with crush wounds reported here.

In no other pathologic condition yet examined is the hypertrophy and granularity of the afibrillar constituent of the juxta-glomerular constituent of the juxta-glomerular apparatus so marked. The fuchsinophil (Masson's tri-chrome stain) granules, generally coarse, dissolve gradually (vacuolar complex of Dunihue and Candon[7]). This process as exemplified especially in one case, is associated with intense vacuolation of the afibril-

[1] Bywaters, E. G. L., and Dible, J. H., *J. Path. and Bact.*, 1942, **54**, III.

[2] Goormaghtigh, N., *Arch. Biol.*, 1932, **43**, 575.

[3] McManus, J. F. A., *Lancet*, 1942, **2**, 394.

[4] Siegmund, H. *Verhandl. Deutsch. Pathol. Gesellsch.*, 1925, **20**, 260.

[5] Zimmermann, K. W., *Z. f. mikr. Anat. Forschg.*, 1933, **32**, 176.

[6] Graef, I., *Am. J. Path.*, 1943, **19**, 121.

[7] Dunihue, F. W., and Candon, B. H., *Arch. Path.*, 1940, **29**, 777.

lar cells. Pycnosis and shrinkage of the afibrillar cells is sometimes observed.

This afibrillar and granular transformation of the cells of the media of the preglomerular arterioles is a distinctive feature of the anuric kidney. The interlobular arterioles may also be involved. These afibrillar cells are as a rule in marginal position except at the arteriolar bifurcations where they are found immediately under the endothelium. Where this transformation is very extensive, it leads to the almost complete disappearance of the fibrillar muscle cells. The lumen of the arterioles is then wide and filled with stainable serum.

The intimal granulomas (Siegmund)[4] of the interlobar veins, contain histiocytes, large cells of which the origin is not yet determined, spindle cells (muscle and connective tissue cells), red blood cells, blood platelets, fibrin and a hyalin substance. The endothelium is hyperplastic and later undergoes fibrinoid necrosis. The granuloma then becomes a mural, fibrinoid thrombus. The histogenesis of these intimal granulomas has been demonstrated. (Siegmund[4] and Kusama).[8]

Discussion. The vascular changes reported here are very similar to those observed in eclamptic anuria. In such cases Goormaghtigh[9] found that the glomerular tufts were ischaemic but unaltered in their structure, and that there was marked afibrillar transformation of the pre-glomerular arterioles. The granularity of the afibrillar cells was, however, not so pronounced as in the "crush-syndrome" cases. A great similarity exists also with very acute fatal glomerulo-nephritis (Volhard,[10] Goormaghtigh[2]). Moreover this granular transformation of the preglomerular arterioles is the distinctive feature of the ischaemic kidney of the rabbit in the Goldblatt experiment (Goormaghtigh),[11] and, according to this author, plays an important part in the production and liberation of the vasopressive substance formed in increased amount in the ischaemic kidney.[10-12] If this premise is correct, there is reason to believe that in "crush-injury anuria," this vasopressive substance is liberated in excess and causes a persistent spasm at the vascular pole of the glomerular tufts so long as contractile cells persist in the arteriolar wall or in the glomerular tuft.

The concept of the existence of vascular spasm is perhaps corroborated by the presence of the intimal granulomas noted in the interlobular veins. It is well known that these granulomas appear in allergic conditions (Siegmund,[4] Aschoff,[14] Rössle[15]) and the latter, it is generally agreed, are characterized notably by localized, excessive vascular spasms.

As to the cause of the enhanced endocrine vasopressive reaction (Goormaghtigh[13]), of the renal arterioles, local anoxia, associated with the extensive muscular alteration, seems to be the determining factor (cf. the cytology of the ischaemic kidney). Nevertheless the effect on the afibrillar cells of the pathologic glomerular filtrate (Bywaters & Dible[1]) acting via the macula densa (Zimmermann[5]), or via the severely altered tubular cells[1] in contact with the arterioles, must also be considered.

Summary. In 4 instances of fatal, so-called renal crush syndrome in man, study at necropsy disclosed glomerular ischemia or oligemia; enlargement of the juxta-glomerular apparatus with increased granularitv of the cells, hyperplasia and hypertrophy of the afibrillar (granular and non-granular) cells of the media of the pre-glomerular arterioles. In 2 of the 4 cases, intimal granulomata and parietal thrombi were found in the interlobular veins. Since similar changes are

8 Kusama, S., *Beitr. path. Anat.*, 1913, **55**, 459.

9 Goormaghtigh, N., *Bull. Acad. Roy. Med. Belg. VIe. serie*, 1942, **7**, 194.

10 Volhard, F., *Handb. innere Mediz. 2e. aufl.*, **6**, Berlin, J. Springer, 1931.

11 Goormaghtigh, N., PROC. SOC. EXP. BIOL. AND MED., 1939, **43**, 575.

12 Goormaghtigh, N., and Grimson, K. S., PROC. SOC. EXP. BIOL. AND MED., 1939, **42**, 227.

13 Goormaghtigh, N., *La fonction endocrine des artérioles rénales*, Librairie Fonteyn, Louvain, 1944.

14 Aschoff, L. *Verhandl. Deutsch. Path. Gesellsch.*, 1925, **20**, 272 (discuss. Siegmund).

15 Rössle, R., *Virchow's Arch.*, 1933, **288**, 780.

found in ischemic (Goldblatt) kidneys, in which the author postulated an endocrinologic role for the affected cells, consisting of the liberation of a vasopressor substance, it is suggested that similar liberation of a vasopressor substance occurs in the anuric crush syndrome, causing arteriolar spasm at the vascular pole of the glomerular tufts.

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Potentiating Effect of Anaphylactic and Histamine Shock upon Herpes Simplex Virus Infection in Rabbits.*

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A rabbit which had been inoculated intramuscularly and again intracerebrally with herpes simplex virus suspension with no apparent infection was, after a period of 6 months, sensitized to egg-white and thrown into anaphylactic shock. On the seventh day following the shock, the first symptoms of herpetic encephalomyelitis appeared. On the ninth day the animal was moribund and was dispatched.

Protocol—Rabbit G 126.

7/30/44	Inoculated with 1 cc 10% mousebrain suspension of H.F.$_{12}$ virus into quadriceps femoris muscle of right leg.
7/31 to 8/28	Daily temperatures normal.
8/28	Intracranial inoculation with 0.2 cc 10% suspension of same virus. No illness followed this inoculation.
1/23/45	5 cc egg-white injected subcutaneously into right hind leg.
1/25	2 cc 10% egg-white in distilled water intravenously.
2/ 6	0.75 cc egg-white intravenously; severe anaphylactic shock ensued.
2/ 8	Animal well.
2/ 9	No change.
2/10	No change.
2/13	Animal depressed RT. 104.9.
2/14	Rectal temperature 106.2. Severe opisthotomy, grinding of teeth, twitching of facial muscles, excessive salivation, head nystagmus, excitement noted.
2/15	Condition worse. Animal killed. Autopsy revealed extensive encephalomyelitis with typical herpetic inclusion bodies.

* Aided by a grant from the National Foundation for Infantile Paralysis.

Trauma, intracerebral injections of irritating solutions, and extensive subcutaneous inflammation have been shown by Le Févre de Arric and Millet[1] to increase the susceptibility of rabbits to intravenous inoculation with Herpes simplex virus.

The history of rabbit G 126 and the reports in the literature, cited above, have led us to the following experiments which were designed to test the potentiating effect of shock upon susceptibility to intravenous inoculation with the virus of Herpes simplex. Histamine shock has been substituted for anaphylactic shock.

Experiment I. Six young adult rabbits (2.5-3.0 kg) were inoculated intravenously with 1 cc of the supernatant of a centrifuged 10% infected mouse brain suspension in Locke's solution.‡ Three of the animals (G 136, 137, 138) had been subjected to severe anaphylactoid shock 10 minutes previously by the intravenous injection of 2.75 mg of histamine diphosphate. The other 3 animals (G 139, 140, 141) were given no other treatment. Of the 3 animals in which

[1] de Févre de Arric, and Millet, M., *C. R. Soc. Biol.*, Paris, 1925, **93**, 45; 1926, **94**, 782.

† Bio-assays of these 2 animals revealed virus in the midbrains and spinal cords of each; the livers, kidneys, spleens, and adrenals were negative. The virus which was recovered had, after the second mouse passage, the same m.l.d.$_{100}$ as the original infective dose.

‡ The Herpes simplex virus used in these experiments was maintained by intracerebral mouse to mouse passage. The m.l.d.$_{100}$ was 0.03 cc of a 1/10000 suspension of the brain.