

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Neumann HPH, Vortmeyer A, Schmidt D, et al. Evidence of MEN-2 in the original description of classic pheochromocytoma. *N Engl J Med* 2007;357:1311-5.

SUPPLEMENTAL MATERIALS

1. The four physicians involved in the Report of 1886

The 1886 Fränkel report shows the names of four physicians, including himself: Hofrath Rudolf Maier, Professor Max Schottelius, and Hofrath Wilhelm Manz. We gathered further details for these four individuals by contacting the Institute of History of Medicine, the University Library in Freiburg and through letters to their relatives.

Hofrath Rudolf Maier (1824 -1888), Professor of Medicine, carried out the proband's autopsy. He introduced pathology as an independent discipline at the University of Freiburg, founded the Institute of Pathology and was the first director from 1883 until 1888. Maier's arguably most well known publication was the description of periarteriitis nodosa together with Alfred Kussmaul, the director of the University Hospital of Internal Medicine in 1866¹.

Professor Max Schottelius (1849-1919), who examined the tumors with Maier, moved in 1883 to Freiburg as a Professor Extraordinarius at the Institute of Pathology, founded the Institute of Hygiene and held the chair of this institute until retiring in 1912.

Hofrath Wilhelm Manz (1833 - 1911), who examined the retinae and eyes at

autopsy, was the founder and first director of the University Eye Hospital in Freiburg during the period 1868 to 1901.

Felix Fränkel was a physician at the University Hospital in Freiburg. The publication in 1886 shows the remark “dissertation”. We therefore surmise that Dr. Fränkel was a relatively young physician. Unfortunately, no information could be achieved.

The four major clinical “players” were academic physicians in a university hospital setting. At least three were full professors and leaders of their departments or institutes, and clearly leading lights in their respective fields at that time. Two of the four were bestowed the highly honored title of “Hofrath.” By all accounts, therefore, all four academic clinicians were well-respected experts in their fields, and hence, their observations highly credible.

2. Translation of Hofrath Maier’s Handwritten Autopsy Report on Minna Roll

Minna Roll 18yr. Deceased December 20 (1884) 8.30 a.m. Autopsy December 21, 11 a.m.

Nephritis parenchymatosa acuta. Hemorrhages in most organs. Tumor of the left adrenal gland.

Medium height. Rather sturdy cadaver of pale skin color. Intense death mask. The visible mucosae are livid. Pupils symmetric. Moderate goiter. Well developed breasts.

Abdomen sunk in. No anasarca. Cranium very thick, pia slightly cloudy. Little fluid in the ventricles, brain substance rather consistent, otherwise nothing abnormal.

Heart weight 320 g. Upper lung margins normal, no content and no adhesions in the pleural cavities. Little fluid in the pericardium. The heart cavities are tightly filled. Right ventricle normal. Right atrium insignificantly dilated. Extensive hemorrhages in the media and adventitia in the beginning portions of the pulmonary artery. Left atrium normal. Extensive hemorrhage in the endocardium of the left ventricle and the superficial muscle layers. Aortic wall slightly thickened, otherwise no changes.

The pleura of both lungs is smooth, shiny, and shows no hemorrhage. Lung tissue normal, only increased blood content in the lower lobes. Somewhat bloody mucus in the bronchi.

Abdominal viscera normal. No fluid in the peritoneal sac.

Spleen of normal size, capsule smooth and shiny, parenchyma very soft.

Liver of normal size, rather soft, otherwise nothing abnormal. Somewhat dark bile in the gall bladder and several raspberry-shaped gallstones.

A fist-sized tumor is found above the upper end of the left kidney, loosely tighted with it by connective tissue; this occupies the site of the left adrenal gland. On gross sectioning, it appears of a brownish-gray color, amber-coloured especially in the middle parts. Some blood-filled cysts are also to be found in it.

The left kidney of normal size, rather consistent, the Malpighian bodies very distinct.

Numerous hemorrhages in the mucosa of the renal pelvis.

Similarly in the right kidney. There is a small hazel nut-sized soft nodule in the right adrenal gland.

In the mucosa of the urinary bladder also extensive hemorrhage.

In the uterus, a slightly bloody mucous plug. Uterus anteflexed, adjacent to the posterior bladder wall.

Little content in the intestines, rather extensive hemorrhage throughout the intestinal mucosa, except in the colon.

Microscopic examination. The kidneys show only intracellular edema and degenerative vacuolation of tubular epithelia.

3. Histology of Adrenal Tumors and Retinae (Extracted & Translated from Felix Fränkel's Report)

The investigations have been performed by Hofrath Maier and Professor Schottelius.

Of the left adrenal tumor, one half was fixed in alcohol, the other in Müller's fixative (Potassium 2.5 g, sodium sulphate 1 g, aqua dest. 100 ml) and embedded in celloidin.

Slides were stained with hematoxylin, neutral carmine, lithium carmine, gentian violet, and osmic acid. Microscopic examination showed numerous smaller or larger vessels and blood spaces, which either had no wall, directly bordered on the cell masses of the tumor, or with only one endothelial layer. Thus a completely constructed network came about, which in part was comprised of already formed, or forming, vessels.

Large cells with occasional large nuclei could be found in the tumor, which contained light yellow to brown pigment. There were giant cells with fine-granular cytoplasm and several large nuclei, each of which with one to three small nucleoli. Furthermore, there

were large spindle cells with granular protoplasm, but only one large nucleus and nucleolus. In some areas cells seem to be arrayed in an apparently alveolar arrangement, some pigment-containing, some pigment-free.

The right adrenal tumor was entirely hardened in Müller's fixative* and embedded in celloidin. It was surrounded by adrenal substance in tube-shaped arrangement. Also this tumor contained large cells rich in protoplasm with one or more large nuclei thoroughly resembling (adrenal) medullary cells. The nuclei in part were twice or three times the size of those in normal (adrenal) medullary cells. Cell arrangements recalled the form of complexes in the normal medulla, but often lost the typical form the closer to the center of the tumor. Here, spindle cells dominated. Along the boundary between tumor and normal tissue, very circumscribed small cell infiltration foci in the vessels are shown which in other parts had partially or completely transformed into connective tissue. At individual places such accumulations directly made the impression of small fibroma nodules.

The retina, investigated by Hofrath Manz, revealed extensive multi-focal hemorrhage and inflammatory deposits in the intermediate granular layer, in addition to thickened

and sclerosed nerve fibers.

* Müller's fixative contains potassium 2.5 g, sodiumsulphate 1 g, aqua dest. 100 ml.

References

1. Kussmaul A, Maier R. Über eine bisher nicht beschriebene eigenthümliche Arterienerkrankung (Periarteriitis nodosa), die mit Morbus Brightii und rapid fortschreitender allgemeiner Muskellähmung einhergeht. Deutsches Archiv für Klinische Medizin 1866;1:484-518.