THE RELATION OF VON RECKLINGHAUSEN'S DISEASE (MULTIPLE NEUROFIBROMATOSIS) TO GIANT GROWTH AND BLASTOMATOSIS

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It is at present generally considered that Von Recklinghausen's disease (multiple neurofibromatosis) depends on a congenital anomaly in the development of the nervous system. Whether the cells of Schwann proliferate to form a neurinoma (Verocay) or whether the epi-, peri-, and endoneural connective tissue is partially or entirely responsible for the tumor growth, is as yet unsettled. It seems, at any rate, that a congenital anomaly of the ectodermal-mesenchymal components of the nervous system must be reckoned with.

This disturbance is not limited to the peripheral nervous system but may involve the cerebro-spinal axis and meninges as well. Glioma, heterotopia of the gray matter, endothelioma of the dura or leptomeninges, etc., have been observed. Indeed the dysontogenesis, as Adrian first emphasized, may even extend beyond the peripheral and central nervous system, and occur in other organs of the body. Von Recklinghausen's disease may be combined with epispadias, cryptorchism, uterus bicornis, renal malformations, polythelia, malformations of bones or muscles, dwarfism, infantilism, etc. The recent research of Geert Hoeckstra on the inheritance of this disease also supports the idea of a dysontogenetic origin in von Recklinghausen's disease.

Multiple neurofibromatosis then is apparently related in its genesis to various affections of other organs of the body. The recent work of L. Pick, Oberndorfer, A. Schultz, and Schmincke, calls to our attention a more accurate relationship between neurofibromatosis and changes in a particular organ.
L. Pick was the first to show that there occurs in the small intestine of the horse a partial giant growth which bears a very close relation to a neurofibromatosis of the corresponding mesenteric sector. The cases of Oberndorfer, A. Schultz, and Schmincke involved the human appendix. Oberndorfer's case of a giant appendix with neurofibromatosis of its mesentery resembles in most details the findings in the following case described by Pick who has recently studied the combination of giant growth of the intestine and mesenteric neurofibromatosis. A sharply delineated segment of gut 50 cm. in length presented enormous increase in thickness. Leading up to this segment there is a moderate widening of the lumen and some hypertrophy of the muscle coats resulting from stenosis of the lumen in the giant part. The histological examination and measurement show that all layers of the intestine participate in the giant growth in proportion to their normal width. It, therefore, appears as if an intestinal segment from some giant animal had been incorporated in the horse's intestine. This is, therefore, an actual partial giant growth of the intestine perhaps the most perfect form of true giant growth of a soft part of the body that has as yet been described.

This growth is circumscribed and in exact correlation with a neurofibromatosis of the innervating splanchnic nerve-branches. The latter form a fan shaped neurofibroma which definitely limits the giant growth to the adjacent intestinal wall. This extends from a point in the mesentery towards the lumen.

Further microscopic examination shows that there are present around the convoluted neurofibroma a number of branches of the mesenteric nerves not involved in the tumor formation but showing instead a true nervous hyperplasia. Within the giant intestine itself, the sympathetic intestinal plexuses—the myenteric as well as the submucosal (Meissner's)—present a giant development.

Finally there is some blastomatosis of the cells of Schwann (i.e., neurinomatous changes) not only involving the finer nerve-branches of the intestinal serosa, but also the hypertrophic branches of the mesenteric plexus and the branches of the
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submucosal giant plexus. Thus, in the entire sector of intestine and mesentery there is a mixture of giant growth and neurofibromatosis. In the mesentery the neuroblastomatosis predominates and in the intestine the giant growth.

As mentioned above, there is a definite agreement between these findings and those observed by Oberndorfer in the giant human appendix. A. Schultz describes a giant growth and neurinomatosis of the nerve plexus of the appendix without giant growth of the intestine itself. In Schmincke's case the marked thickening of the appendix, which projected into the cecum, no doubt resulted from a neurinomatosis of the nerves in the wall and mesentery of the appendix but here also there was no giant growth of nerves or intestine.

L. Pick leaves it an open question as to whether the changes observed by A. Schultz and Schmincke are not changes in the nervous apparatus accompanying chronic inflammation of the appendix.

If the observations of A. Schultz and Schmincke belong to the class under consideration, we have a graduated scale in the intensity and completeness of the change, as follows:

1. Giant growth and neurofibromatosis (neurinomatosis) of the intestinal nerves, giant growth of the intestine itself; giant growth and neurofibromatosis of the nerves of the corresponding mesentery (case of L. Pick).

2. Giant growth and neurofibromatosis (neurinomatosis) of the intestine combined with giant growth of the nerves of the adjacent mesentery (case of Oberndorfer).

3. Giant growth and neurinomatosis of the nerve plexus of the intestine without giant growth of the intestine itself, apparently also without changes in the mesentery (case of A. Schultz).

4. Pure neurinomatosis of the nerves of the intestine and adjacent mesentery without giant growth of the nerves or intestine (case of Schmincke).

It is evident that the individual cases in this series show successively less changes; hence it is logical to suppose that cases with even slighter changes do occur.
As L. Pick has shown, the individual forms of giant growth are sometimes combined with true neoplasms—angioma, lipoma, etc.—especially in the region of the growth itself. If we could prove that these new growths as well as the giant growth were congenital, then the blastoma could be considered a partial giant growth of a single tissue associated with the partial giant growth of an organ. Theoretical considerations would make a sort of scale here also plausible, for it is possible that giant growth and neurinomatosis of the splanchnic region or a pure neurinomatosis could occur without a corresponding giant growth or a neurinomatosis of the related intestinal segment. Indeed, instead of this, neoplasms of another sort might occur here without a simultaneous giant growth of the intestinal segment itself. Such tumors would be in the topographical union with the changes in the innervating intestinal nerves. It would be especially noteworthy if the blastoma in its own special way also indicated an "anlage" defect as its origin. That this theoretical deduction has an actual basis will be shown in the following observations made on the autopsy material of Prof. L. Pick in the Pathological Institute of the Friedrichshain Hospital in Berlin, with whose kind assistance I have studied this material.

History. The case is that of a man sixty years old, admitted to the surgical service of Friedrichshain Hospital February 13th, 1922. His family and past history was negative, except for one attack of rheumatic fever. He had been alcoholic. A year prior to admission, symptoms of the present disease began with variable periods of sharp abdominal pain. The symptoms became marked six weeks prior to admission, when he began to have diarrhoea, rectal incontinence, tenesmus, and periods of obstipation. Treatment at home was ineffectual and he was referred to the hospital. The patient had persistently lost weight in the past year.

Physical examination. Examination on admission revealed a poorly nourished, pale, elderly man.

The abdomen was distended and rigid, and palpation elicited marked tenderness in both lower quadrants, especially the right, where a definite resistant lumpy mass was felt. There was also resistance in the rest of the lower abdomen. The liver and spleen
were normal in size. The anus was puffy and swollen, and the tissue surrounding it infiltrated, oedematous, and lumpy. On either side of the anus was a pencil-sized perforation.

The nervous system showed no pathological findings.

The rectal wall bled easily, was thickly infiltrated, and the ampulla filled out with a soft tumor mass. Most resistance was felt in the right upper segment.

*Course of illness.* The symptoms were a continuation of those described—diarrhoea with thin watery blood-tinged stools, continuous incontinence and tenesmus, abdominal pain.

*Laboratory findings.*—Urine: acid, albumin and sugar not present. No urobilin, urobilinogen, bilirubin, or diacetic acid were found. Indican was slightly increased. Blood examination: HB 56 per cent; R. B. C. 3,200,000; color index 0.8 Indican positive in the urine. Later Bac.-coli communis was found in the urine and considerable amounts of albumin and many leucocytes.

Thirteen days after admission the patient developed a temperature of 100.6° F., and the following week he began to show signs of pulmonary involvement. In the left interscapular space the percussion note was impaired; higher up dullness and bronchial breathing; in the right lung posteriorly diminished resonance as high as the superior angle of the scapula. At the same time a bed sore began to form over the sacrum. Later a gangrenous area developed.

Six weeks after admission the patient developed oedema of the legs and back, and two months after admission succumbed to his illness.

*Autopsy findings* (Prof. Dr. L. Pick): Body measures 176 cm., poorly nourished, Musculature and fat are scant. Decubitus sore 12 cm. in diameter over the sacrum, dark greyish green discoloration and bone exposed. Extensive phlegmonous infiltration of both gluteal muscles, and oedema of both legs and scrotum.

Lungs: Both lungs contain air and are oedematous, the lower lobes very hyperaemic. In one of the main branches of the left pulmonary artery there is a reddish-white thrombus 2 cm. long.


Spleen soft, pulpy, bluish-red on section.

Other unimportant lesions are summed up in the anatomical diagnosis.
The caecum, as well as the appendix and ascending colon, is elevated by a convoluted retroperitoneal mass, which is double the size of a man’s fist. This mass (see Fig. 1, \textit{knt}) is tough, elastic, greyish white and connected with other similar retroperitoneal masses visible through the peritoneum. Other tumors of smaller size extend downward to the pelvic minor. Detailed dissection shows:

1. All the tumors are connected by strands (\textit{str}) the size of the little finger or somewhat smaller. These strands are of similar color and consistency.

2. The entire group of tumors and strands—in all its aspects—represents the completely changed right lumbar plexus. Below Poupart’s ligament, and connected with the above masses, are found nodular tumors (\textit{knt}), approaching the size of a pigeon’s egg. These represent the right femoral nerve and its branches in this region.

The entire mass of tumors and strands as dissected out is shown in the picture in Fig. 1.

Adherent to the ileo-inguinal nerve, which is unchanged in its course, is a walnut-sized, ellipsoid, grayish white, isolated tumor. The lumbar plexus on the left side is unchanged; likewise both sciatic nerves. The right femoral nerve, below the tumor described, along with all the remaining large nerves of both legs, shows nothing pathological; likewise the nerves of the cervical and brachial plexuses. The right lumbar plexus, carefully dissected, is in all its parts so entirely changed by strands and tumors that it is impossible to identify with certainty the particular roots or nerves.

The most voluminous tumors are situated proximally. The largest of these measures $18 \times 12 \times 7$ cm. (i.e. twice the size of a man’s fist). Below follows a tumor measuring $14 \times 5\frac{1}{2} \times 4\frac{1}{2}$ cm. (see Fig. 1). On cross section the tissue is whitish, in part fascicular, elsewhere oedematous and even gelatinous.

The right femoral vein is thrombosed to 15 cm. below the saphenous opening—partly by reddish and partly by lighter firmly adherent masses.

The left femoral vein is in its middle third almost fully occluded by firmly adherent dark red thrombi.

On the head of the right epididymis (Fig. 2) there is a group of small transparent cysts (\textit{eye}) approximately the size of a walnut. Smaller transparent tumor nodules on the fine nerve branches (\textit{smn}) accompanying the vas deferens (\textit{fs}) present themselves in pearl-like rows. They range in size to that of a lentil, and larger, and are greyish
Fig. 1. The dissected right lumbar plexus in neurofibromatous degeneration. 
Kn, nodular tumor (uppermost part of the plexus); Knii, smaller nodular tumors (toward right inguinal region); Str, strands connecting nodules.

Fig. 2. Right testicle (t) and funiculus spermaticus (fs). Cyc, cystic tumor of the head of the right epididymis (snn), pearl-like nodules of the sympathetic spermatic nerves.
white in color. That they are softened tumors is evident from the presence of solid whitish particles.

The pelvic organs are difficult to remove. The bladder and rectum are surrounded on both sides by very tough convoluted masses (Fig. 3, pnt); the largest of these are the size of a pigeon’s egg. The tumors are adherent to the bladder and rectum on the one hand and to the pelvic wall on the other. Finer dissection shows that these tumor masses represent the pelvic nerve plexus, i.e., the branches supplying the bladder and rectum. These nerves are entirely lost in the tumor mass. The consistence, color, and cross section of these tumors is similar to that of the lumbar plexus tumors previously described. The ureters (ru, bu) which pass through the tumor mass, are not dilated; the bladder and ureteral orifices are normal; likewise the pouch of Douglas, the prostate, the seminal vesicles, the sacral plexus and its main branches, and the sciatic and pudendal plexuses.

Around the most distal rectal segment is a circumscribed phlegmonous infiltration corresponding to the perforations on each side of the anus; the infiltration does not reach any higher.

The rectum contains no unusual products. The mucous membrane (mm) is pale and smooth and lies in longitudinal folds. Eight cm. above the anus a very marked change begins in the mucous membrane. This change involves the whole area as far down as the anus. The beginning of this change, encircling the intestinal lumen, corresponds to the exact place where the tumor masses firmly impinge on the rectal wall and unite with it (see Fig. 3). From here to the anus the entire mucous membrane is transformed into a coarse papillary, rather pale tumor-like mass which is, in parts, gelatinous (pv). The coarse papillary prominences often carry with them smaller villi, variable in form and number, so that a form of branching results. The vegetations float in running water. On section, the tissue of the plump papillary masses is everywhere demarcated from the rest of the intestinal wall.

The separation from the upper rectum is sharp, except that the longitudinal folds of the mucous membrane gradually run into the papillary elevations (Fig. 3).

The wall of the upper rectal segment is of normal thickness and all its layers are easily distinguishable. The wall of the lower rectal segment is four times the normal thickness, devoid of definite layers, and inseparable from the neighbouring tumor nodes and strands.
The rest of the large intestine, including the appendix, is negative; likewise the mesentery, the mesenteric lymph nodes, as well as the main branches and trunk of the portal vein.

Brain and leptomeninges are negative.

ANATOMICAL DIAGNOSIS

Phlegmonous infiltration of the gluteal regions of both sides, gangrenous sacral decubitus, ulcerating perianal phlegmon; fresh verrucous
endocarditis on mitral and aortic valves, marked dilatation of both ventricles, fatty metamorphosis of the heart muscle, acute splenic tumor, thrombosis in a branch of the left pulmonary artery; recent thrombosis of the left femoral vein, earlier thrombosis of the right.

Multiple voluminous neurofibromata of the entire right lumbar plexus and its main branches as far as Poupart's ligament; neurofibromatosis of the entire sympathetic pelvic plexus, especially around the bladder and rectum; neurofibromatosis of the plexus of the vas deferens.

Voluminous papillary growth of the mucous membrane of the lower rectal segment with thickening of the entire wall.

Left hydrothorax, oedema of the scrotum and of both legs. Slight arterio-sclerotic nephrosclerosis, small cysts and adenoma in the cortex of the right kidney, slight cirrhosis of the liver and small cavernoma, small calcium deposit in the left lobe of the thyroid, anthracosis of the tracheo-bronchial lymph nodes.

Microscopical observations: After hardening the material in 10 per cent formalin, frozen and paraffin sections were stained with hematoxylin, eosin, with Van Gieson, and with Biechowsky's method for axis cylinders.

The examination shows:

1. Nodular masses of the neurofibromatosis of the right lumbar plexus and of the hemorrhoidal plexus.

Corresponding to the macroscopic impression the tumors are mainly myxofibromatous. In large areas there are delicate collagen fibrils pressed apart by transparent fluid (oedema). Between the fibrils and in some places connected with them are small stellate and spindle shaped cells, and also many round ones. In gradual transition from this area are interlaced fibrillar connective tissue bundles, containing fairly numerous long nuclei. All these fibrils take a red stain with Van Gieson. Here and there within this tissue there appear areas especially rich in nuclei and with well-developed finely fibrillar intercellular substance. The nuclei have a pronounced spindle shape and are parallel to the direction of the fibrillar bundles. Besides the spindle forms of nuclei there are voluminous round ones exceedingly rich in chromatin. Sometimes four or five nuclei lie close together in a sort of cell nest.

2. These relations, especially the red staining of the delicate fibrils with Van Gieson become still more pronounced in the sections from the tumors of the hemorrhoidal plexus. The larger nodules show a
myxofibromatous structure like that of the large tumors from the lumbar plexus. On the other hand the fine macroscopically invisible branches of the sympathetic, without exception blastomatous, give an entirely different picture. Here one sees enclosed in purely fibromatous fasciculi, bundles of the finest fibrils, which in contrast to the surrounding red collagen fibrils, stain exquisitely yellow. They are accompanied by very many spindle-shaped and also round nuclei. Not infrequently we see, on transverse section of these bundles, a concentric arrangement of the cells. At times, too, we meet with some resemblance to the well-known palisade or "parade formation" of the nuclei seen in neurinoma.

3. The nerve bundles accompanying the vas deferens have in some places an enormous volume, and show nearly everywhere the changes of neurofibromatosis and neurinomatosis. Here also are found fibrillar fasciculi, which, on transverse section, show a concentric arrangement of their elements. The nuclei here show some polymorphism; some are spindle shaped, some large, notched, and rich in chromatin.

4. The wall of the rectum above the distal affected segment shows no special changes microscopically.

5. Sections through the entire thickness of the wall of the lowest rectal segment (Fig. 4). Corresponding with the macroscopic findings, the muscle sheaths show extraordinary general hyperplasia. Between the bundles there is often an inflammatory infiltration of small round cells; this is partly diffuse, partly circumscribed—and in other places takes the form of a real granulation tissue.

The papillary membrane vegetations show everywhere the same picture. They are purely adenomatous (mn); the glands approximate each other. The stroma is finely fibrillar and contains numerous spindle-shaped and small round cells. It is, however, to a large extent, reduced to extremely fine septa. The epithelium lining the glands is without exception of one layer. In most places it consists of fairly high cylindrical cells, practically filled with rather long dark staining nuclei. Nowhere is there histological evidence of mucus production, or of any other secretion. Lower epithelial cell forms occur especially where the glands are cystically dilated. This cystic widening is very frequent but nowhere reaches a marked degree. The cysts are filled, partly with globular or finely granular masses, partly with desquamated epithelial cells—round, swollen, and in various combinations. The general form of the glands is everywhere simple tubular, nowhere branched to a greater extent, and never labyrinthine.
In contrast to the macroscopic impression, it is evident from the microscopic examination that the boundary line between the mucous membrane and musculature is not a sharp one (Fig. 4). The glands are intermingled with the inner layers of the muscle (mu) in broad projections along their entire stroma (gs), not only in single form but "en masse."

The submucosa is entirely missing everywhere; the intermixture is, however, everywhere limited to the innermost muscle layers. The main part of the intestinal wall is free from glandular projections.

The nervous apparatus of the rectal wall is partly destroyed by the inflammatory process, and where it is preserved it is nowhere hypertrophic or blastomatous.

According to the microscopic examination, the tumors of the right lumbar plexus and of the cellular pelvic tissue are neurofibromatous, in certain parts myxofibromatous, in other parts neurinomatous. Finally, special attention is called to the delicate fibrils staining yellow with Van Gieson, and their accompanying spindle cells; such pictures are met with in both the nerve tumors, especially in the pelvic connective tissue. The blastomatosis is entirely limited to the lumbar and pelvic sympathetic plexuses. Nowhere in other nerve stems are tumors present.

Noticeably unusual in its outward manifestations is the affection of the lower rectal segment. It is striking on account of its coarse papillary surface, uninterrupted by ulceration. The microscope shows adenomatous structure together with insignificant cysts. The epithelium of the glands and cysts is without exception of one layer. Forms suggesting carcinoma or adenocarcinoma are entirely lacking. The sharp macroscopic demarcation of these papillary masses from the rest of the intestinal wall, is not confirmed by microscopic examination. The submucosa is entirely lacking (Fig. 4), and not only do single glands occasionally penetrate into the innermost muscle layer, but also the adenomatous tissue, glands, and stroma intermingle with the musculature in broad projections and strands. As shown above, this intermixture affects only the innermost layer of the muscular coat. For this reason, and also because of the lack of any metastases, we do not consider it a
carcinoma. The inflammatory infiltration and granulation tissue within the muscle wall is probably secondary in nature and results from the constant pyogenic infection around the anus.

Fig. 4. Microscopic section through a papillary vegetation of the lower rectal segment (Heimatoxylin, Eosin). Leitz, Oc. 2, Obj. i, TL = 150 mm. mm, mucous membrane (submucosa lacking); mu, unstriped muscle; gs, strands of glands and stroma interlaced with the muscular bundles.

Harbitz has previously called attention to the occurrence of carcinoma in cases of multiple neurofibromatosis, but in his cases there is not the close topographical relation between the new growth and the neurofibromatosis which is so striking in our case. Here there is an intimate topographical relationship between the pelvic neurofibroma of the sympathetic and the adenomatous polyposis of the lowest rectal segment. Exactly at the site where the nodules and twisted strands of the neurofibromatous hemorrhoidal plexus are intimately bound to the rectal wall, the papillary tumor formation of the mucous membrane begins. Here the neurofibroma, according to the
current view, is explained on the basis of a congenital defect and this is suggested by the peculiar mixture of mucous membrane derivatives with the inner muscle layers, and the absence of a submucosa. Hence we have apparently a combined defect of the nerves and their connected intestinal segment. Of course, in the region of the pelvic nerves and the lumbar plexus this reaches far beyond the affected intestinal segment. On the basis of this congenital defect, the blastomatosis develops on these nerves as well as in the intestine; it does not, however, involve the nerve branches in the intestinal wall.

The cause of the marked thickening of the muscle wall of the affected rectal segment is not entirely clear. An "anlage defect" or a hyperplasia from the influence of the inflammation around the anus are possible explanations.

No actual giant growth is present; there is instead a syntropic combination of neurofibromatosis with pure blastomatosi, a parallel to the combination of neurofibromatosis and true giant growth; hence this case may be classified in the above-mentioned category. Of course, here also the neurofibromatosis and blastomatosis are in genetic coordination.

Conclusions: There is a close topographical relation and genetic coordination between true giant growth and blastomatosis of an intestinal segment and its corresponding nerves. Our case shows that this relation can occur in the form of a pure blastomatosis of nerves and intestinal segment without giant growth. It presents neurofibromatosis of the pelvic and sympathetic plexuses combined with a very unusual blastomatosis of the lowest rectal segment, namely, papillary adenomatosis of the mucous membrane penetrating into the inner layer of the thickened muscular wall.

REFERENCES