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Reprinted from The Archives of Internal Medicine
February, 1909

CHICAGO:
AMERICAN MEDICAL ASSOCIATION, ONE HUNDRED AND THREE DEARBORN AVENUE
1909

Multiple Neurofibromatosis (Von Recklinghausen's Disease)

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MULTIPLE NEUROFIBROMATOSIS (VON RECKLINGHAUSEN'S DISEASE)

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The occurrence of isolated tumors of nerves is relatively frequent, probably more so than generally supposed, for the reason that in the case of many fibromata, fibromyxomata or other tumors a connection with nerves is not always ascertainable. Most tumors of nerves are fibromata or fibromyxomata. I have studied fourteen such tumors, eight of which were situated in the nerves of the forearm and five in those of the lower limbs. The cases were equally divided between the sexes. Most of the tumors occurred in patients between 20 and 40 years of age, and in some of the cases the tumors developed slowly, in the course of ten to fifteen years. In a woman of 50 years there first appeared a pure fibroma, which was removed by operation. Then repeated recurrent growths appeared which gradually became sarcomatous and caused death ten years after the appearance of the first tumor.

The tumors of the optic nerve, five of which were examined, form a separate group, as they possess both clinical and histologic peculiarities. They are most frequent in children. Four of our cases were in boys, 5, 8, 11 and 13 years old. The first symptoms generally are decrease in vision, pain and increasing exophthalmos. The latter may reach such an extreme degree that the eye actually hangs out of the orbit. The growth is usually rapid, though occasionally it is slow, as in two of our cases in which it required five and seven years respectively. The tumors are located in and on the optic nerve (Fig. 1), which presents a spindle-shaped enlargement tapering anteriorly and posteriorly. As a rule they are well circumscribed and do not infiltrate the eye or other surrounding structures. Metastases and recurrences generally do not occur, hence the tumors are relatively benign. Their histologic structure is difficult to interpret. Most often they have been looked upon as sarcomata with varying types of cells arising from the stroma of the optic nerve. In my opinion it is most probable that they are to be considered gliomata (Figs. 2 and 3), arising from the glia in which the optic nerve fibers are imbedded, and in that case they should be classed together with the retinal gliomata and be separated from the ordinary fibrous tumors of nerves.

The border between the isolated tumors of nerves and von Recklinghausen's disease is formed by cases of multiple neurofibromata without the existence of tumors or pigmentation of the skin or other abnormalities. I have had opportunity to examine two such cases in which re-

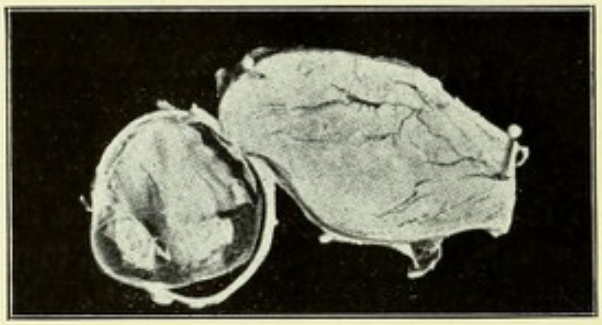

Fig. 1.—Eye with tumor of the optic nerve.

peated recurrences after extirpation took place, sometimes with short intervals, but the tendency to recurrence disappeared and evolution into sarcoma did not take place.

Case A.—A man who at the age of 68 years died of apoplexy, at 45 developed multiple fibromata of the nerves of the left forearm, particularly the ulnar and median nerves and their branches. The tumors gradually caused so much pain

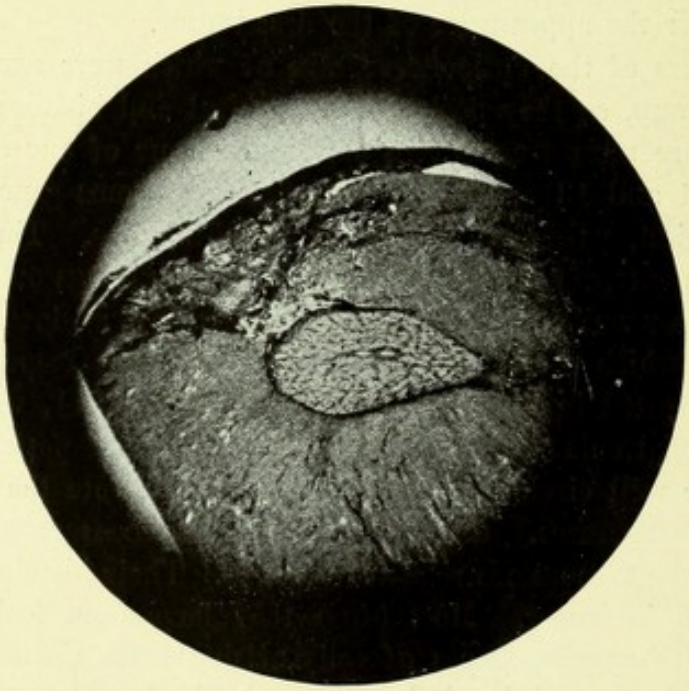

Fig. 2.—Cross-section of optic nerve with tumor. In the center the optic nerve surrounded and compressed by tumor masses.

that in his sixtieth year an operation was performed, when numerous sharply circumscribed tumors varying from the size of a pea to that of a walnut were removed. Recurrences took place a year later and about thirty similar tumors

were removed; a year after this forty or fifty tumors were removed, and finally, one and a half years later, a long, cord-like nerve swelling and several smaller growths were removed from the forearm. All these growths were found to be fibromata rich in cells. The patient then was free from recurrences and free from pain until his death. The family history was negative.

Case B.—In a man who died at the age of 24 years from tuberculosis small tender lumps in one forearm and hand had existed from early childhood. They were most numerous in the median nerve and to a considerable extent had undergone cystic degeneration. At the age of 17 years several of these tumors were extirpated on account of pain, and were found to be fibromata. After a little more than a year recurrence took place and several similar tumors were removed, but from that time on the patient was free from recurrences. In this case there was also no known heredity.

Fig. 3.—Cross-section of optic nerve infiltrated with tumor tissue. Optic nerve to the left; tumor tissue (probably glia tissue) to the right.

Both cases illustrate the tendency to rapid growth and to recurrence soon after operation.

Great interest is attached to those cases of multiple tumors of nerves which are accompanied by a series of other symptoms, showing that we are dealing with a general disease, or constitutional anomaly, if it be desirable to use that term. This is to be inferred, first, because the disease affects more or less extensive parts of the nervous system, hence is

a "system disease," although with variable clinical picture; second, because it is frequently accompanied by tumor formation, and especially pigmentation of the skin; further, because as secondary, less important and less frequent symptoms, we encounter a series of psychic, trophic and vasomotor phenomena. When, in addition to this, in about one-fifth of the cases we find an hereditary basis, the malady either appearing as a family disease or occurring in several generations, although in different forms, it must be admitted that this affection deserves to be

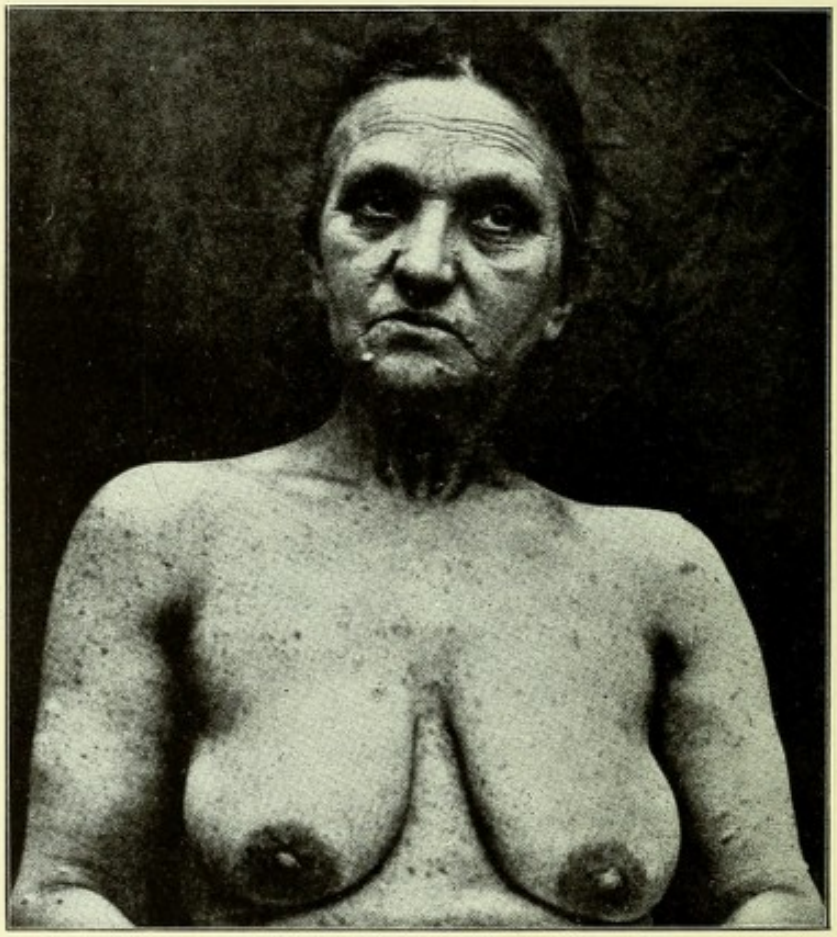

Fig. 4.—Patient 1.

recognized and borne in mind, especially as it is not as rare as might be supposed, particularly if the incomplete forms or *formes frustes* be included.

The disease has been known for a long time. In 1849 the gross anatomic characteristics were described by R. W. Smith.[1] Virchow[2]

1. Smith, R. W.: A Treatise on the Pathology, Diagnosis and Treatment of Neuroma, Dublin, 1849.
2. Virchow: Die krankhaften Geschwülste, 1863.

determined that the tumors originated from the connective tissue element of the nerves. The next advance is associated with the name of von Recklinghausen,[3] after whom the disease later was named. He showed that different forms which until then had been considered separate, really formed a histogenetic unit, especially as in cases of pronounced tumor formation in the skin the tumors were found to develop from the nerves. Later investigators have especially endeavored to establish and describe different types and to study the histologic struc-

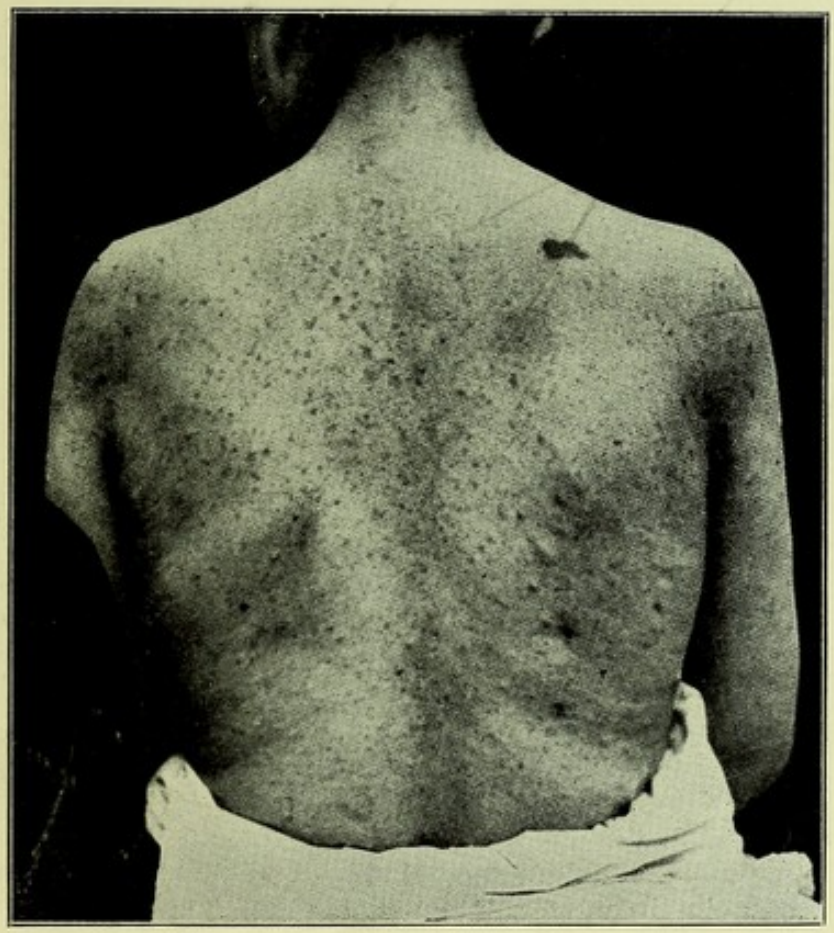

Fig. 5.—Patient 1.

ture. Among later works the monograph of Thomson[4] deserves special mention, and, so far as American literature is concerned, the articles of Prudden[5] and Hektoen and Preble.[6] As I recently had opportunity to

3. von Recklinghausen: Ueber die multiplen Fibromen der Haut und ihre Beziehung zu den multiplen Neuromen, 1882.

4. Thomson: On Neuroma and Neurofibromatosis, 1900.

5. Prudden: Am. Jour. Med. Sc., Phila., 1880, lxxx, 134.

6. Hektoen and Preble: Am. Jour. Med. Sc., Phila., 1901, cxxi, 1.

investigate both the clinical and anatomic details of a number of cases of neurofibromatosis of different types, I will first briefly relate the cases, and later in connection with them make some remarks with special reference to prognosis, symptomatology and histogenesis.[7]

CASE 1.—In a woman 52 years old when observed (Figs. 4 and 5), there had appeared when she was 26 years old, an eruption of fibromata on the chest, back, face, arms and legs. They were soft, not tender, varying in size up to that of a pea; they grew slowly. It was also found that she had numerous pigmented spots all over her body, but there were no tumors on the nerves. The tumors

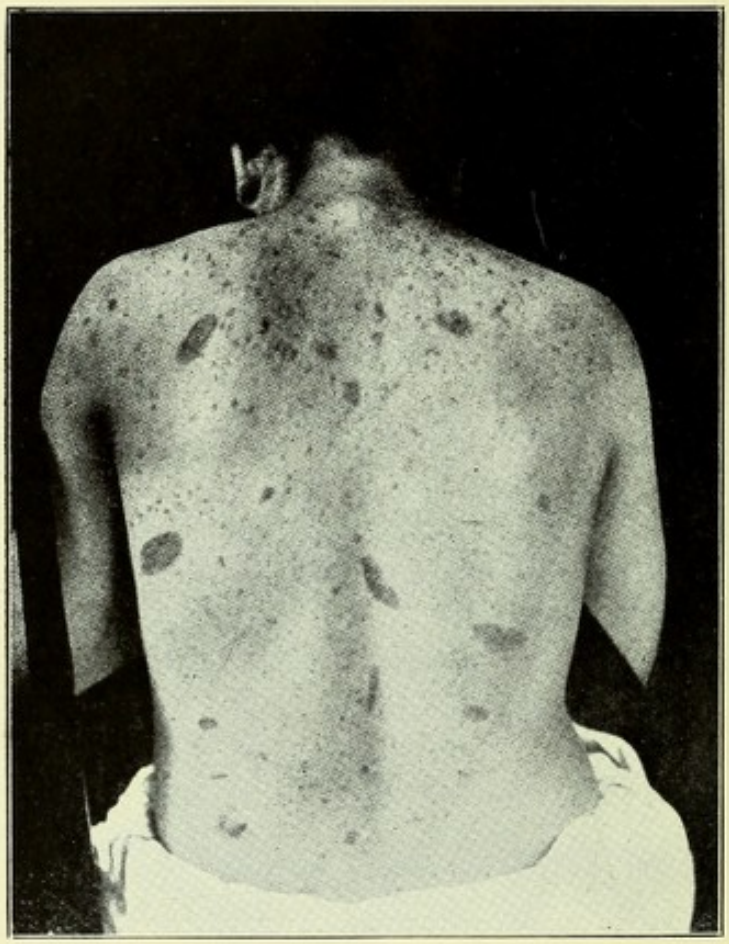

Fig. 6.—Patient 2, daughter of Patient 1.

had the structures of fibroma. On inquiry about the family nothing hereditary was found, but it was learned that her daughter was similarly affected.

CASE 2.—(Fig. 6.) The 23-year-old daughter of the patient just described (CASE 1) had abundant pigmented spots, some of which were freckle-like, others large and light in color, scattered over the entire body. On the back she also had a red angiomatous area, a few soft fibromata and bluish-violet very soft superficial lumps, but there were no growths on the nerves.

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7. Complete description of these cases will appear in Norsk Mag. f. Lægevidensk., Christiania, 1909.

CASE 3.—A woman 36 years old (Fig. 7), of a healthy family, had multiple growths on the chest, back, arms and face, also a few bluish-violet, slightly raised soft patches, and on the left side of the chest a hard pedunculated fibroma of the size of a child's head, the upper surface of which was ulcerated. There were numerous pigmented spots but no tumors of the nerve trunks.

These three cases are instances of the simple form of von Recklinghausen's disease characterized by generally soft, though occasionally hard, cutaneous fibromata and by pigmentary anomalies.

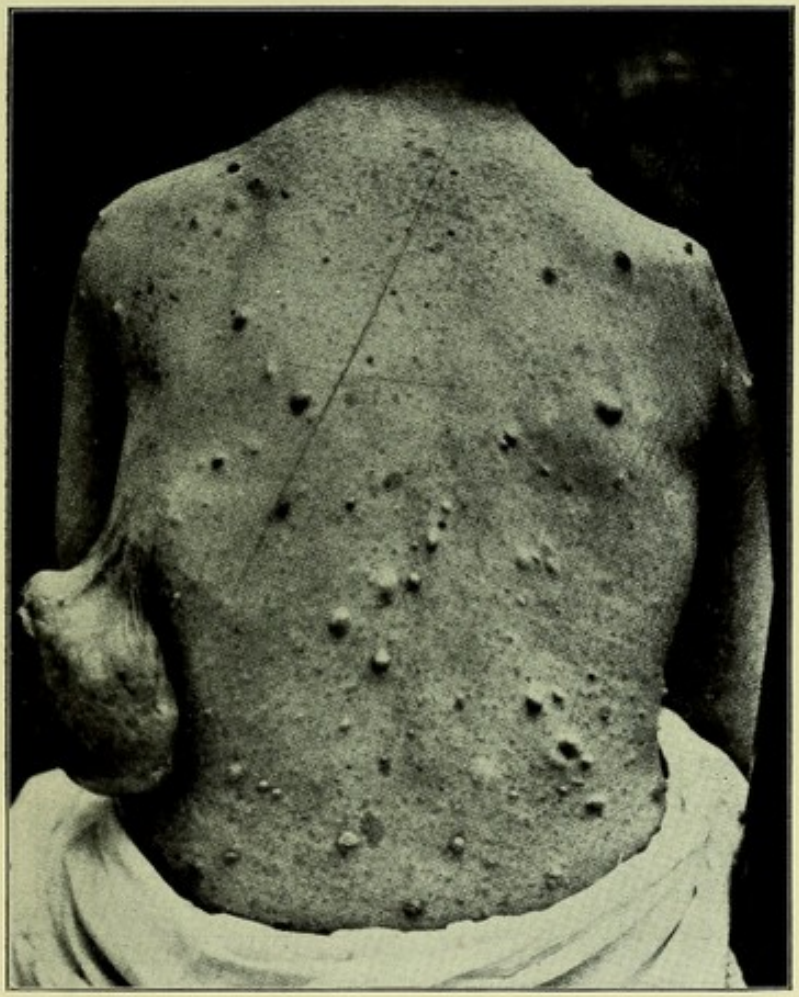

Fig. 7.—Patient 3.

In the following cases there were also multiple neuromata of the subcutaneous nerves:

CASE 4.—A man 28 years old (Figs. 8 and 9) had numerous pigmented spots scatttered on his trunk and limbs. These had existed from birth. The patient also had a large number of soft cutaneous fibromata which had developed after the age of 15 years. On the inside of the right arm were a few hard, tender, spindle-shaped, small fibromata situated on the nerves. On histologic examination of these (Fig. 10) most of the nerve fibers were found preserved as a central

bundle surrounded by proliferated connective tissue arising from endoneurium and perineurium. The only further congenital anomaly which was found was a cryptorchidism.

CASE 5.—A man 55 years old (Figs. 11 and 12), of small, almost dwarf-like stature, had extremely numerous soft cutaneous fibromata, most numerous on the trunk, decreasing in number along the arms and legs. The tumors were partly pedunculated, partly sessile and hemispherical, and reached the size of a walnut. They had been present since childhood but had gradually increased in number and in size. There were also numerous flat, closely placed, bean-sized nodules on the face. He had, moreover, large, brown, oval, pigmented areas and a few small,

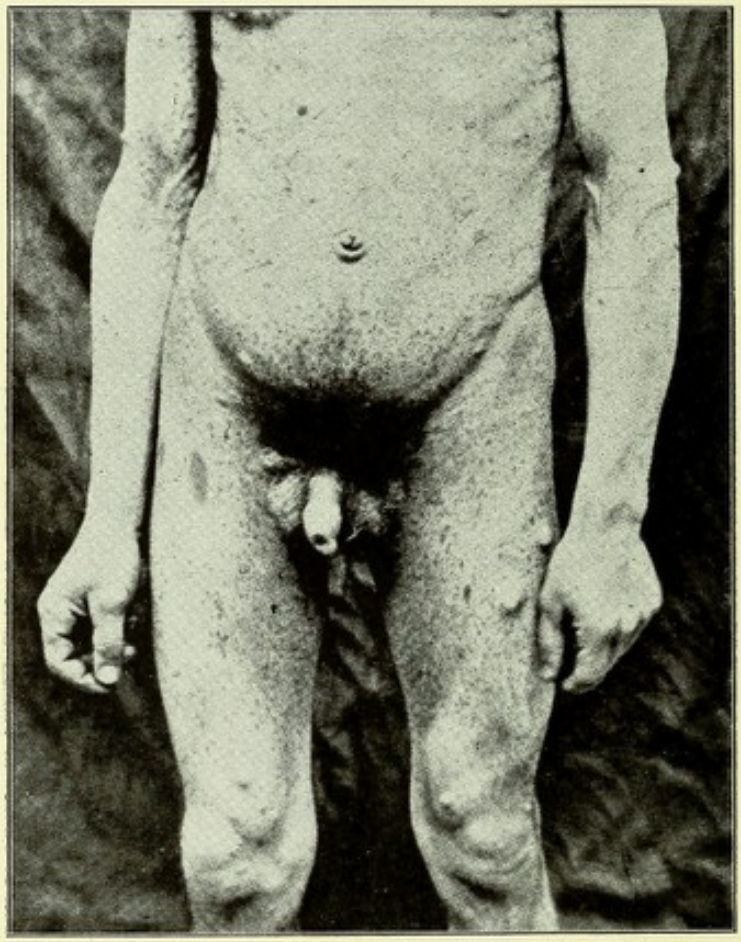

Fig. 8.—Patient 4.

spindle-shaped, somewhat tender nodules of the subcutaneous nerves on the inside of the arm. He gave the impression of possessing little intelligence. No similar cases were known to exist in the family.

CASE 6.—A woman 19 years old had a growth removed which was located in the upper eyelid and the left temple and found to be a racemose neuroma. (*Rankenneurom;* Figs. 13 and 14.) This tumor had appeared in the course of the last two years. She also had scattered, soft, cutaneous fibromata and numerous small and large pigmented areas, said to have been congenital, as well as some areas devoid of pigment which were most numerous on the neck. On both sides of the neck, in the right axilla, and on the inside of the right arm there were a

few tender, spindle-shaped nodules on the nerve trunks. In the following four years, during which I had opportunity to observe her, a small recurrent growth appeared in the eyelid, and during a period of lactation there was an eruption of a large number of small fibromata on the subcutaneous nerves. There was no known heredity.

This case, then, is an example of coexisting racemose neuroma ("Rankenneurom") and subcutaneous neurofibromata in addition to soft fibromata and pigment anomalies of the skin. Judging from the course, the prognosis here was somewhat doubtful.

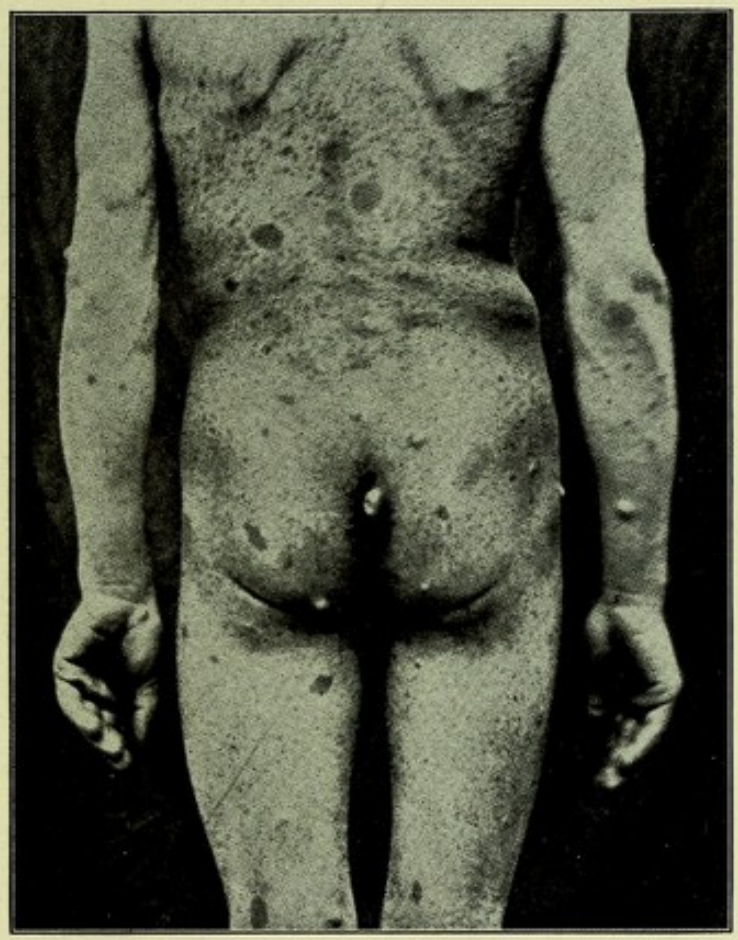

Fig. 9.—Patient 4.

The following three cases illustrate the addition of elephantiasis-like growths:

Case 7.—In a woman 29 years old, of a healthy family, herself an imbecile of the Mongolian type (Figs. 16 and 17), there appeared, at the age of 6 or 7 years, a tumor on the back of the left thigh. This tumor later developed into a large elephantiasis-like growth of the thigh and external genitals of the left side. Later there also appeared numerous small fibromata on the trunk, face and, to some extent, on the extremities, as well as many pigmented areas. There were, however, no demonstrable nodules on the nerve trunks. She was, on the whole,

well built, but slender. The characteristic appearance of the face—oblique eyes far apart, narrow palpebral fissures, broad nose—did not exist from birth but developed at about the age of puberty.

Case 8.—A man, 47 years old (Figs. 18 and 19), of a healthy family, had a congenital growth in the right upper eyelid which gradually spread to form a large, elephantiasis-like mass on the right side of the face, including the right side of the forehead and the right temple. At the age of 8 years it caused blindness in the right eye. At the age of 21 years extirpation was performed and after that time there was little growth. He was not aware of the existence of other tumors, but on examination a number of small fibromata were found on the chest and back and also numerous pigmented areas, some of them very large, chiefly in the *rima inter nates*, and on the hips and thighs, while a few tender string-shaped and spindle-shaped subcutaneous tumors of the nerves of the inside

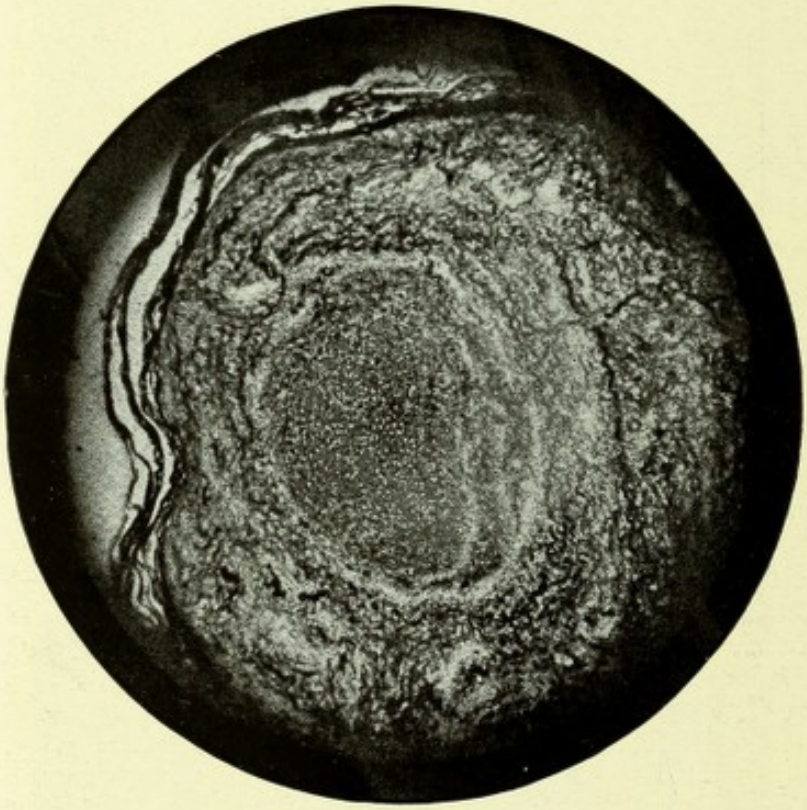

Fig. 10.—Case 4.—Cross-section through a small tumor nodule on a subcutaneous nerve; in the center a large bundle of normal appearing nerve fibers in the periphery of proliferating connective tissue.

of the left arm were also detected. The man had a kyphosis which was said to have developed in childhood; it could not be determined whether this was the result of an old tuberculous spondylitis, or whether, as has been claimed in other cases, especially by French observers, the bone disease had some connection with the multiple neurofibromatosis.

Case 9.—A woman, A. L., 25 years old, who died of erysipelas, had from birth a great fibromatous thickening constituting an actual elephantiasis of the entire left lower extremity (Fig. 20) and of the left side of the external genitals. The thickening had been slowly increasing. The circumference of the leg was 45 cm. and that of the thigh 72 cm. The thickening consisted of fibromatous prolifer-

ation of the cutis and the subcutaneous tissue, the combined thickness of which measured 3.5 to 4 cm. (Fig. 21.) The skin of the left leg was wrinkled, corrugated and shagreen-like. In addition, the skin of the right side of the back and right shoulder showed thickly set, greyish-white, in part very hard nodules; there were no subcutaneous neurofibromata. On the neck there were also leucodermoid areas resembling cicatrices.

A peculiar symptom to be noted was the occurrence, every two weeks since the age of 14, of attacks of trembling and chilliness, with subsequent sensation of heat and sweats. It was learned that similar elephantiasis of the lower ex-

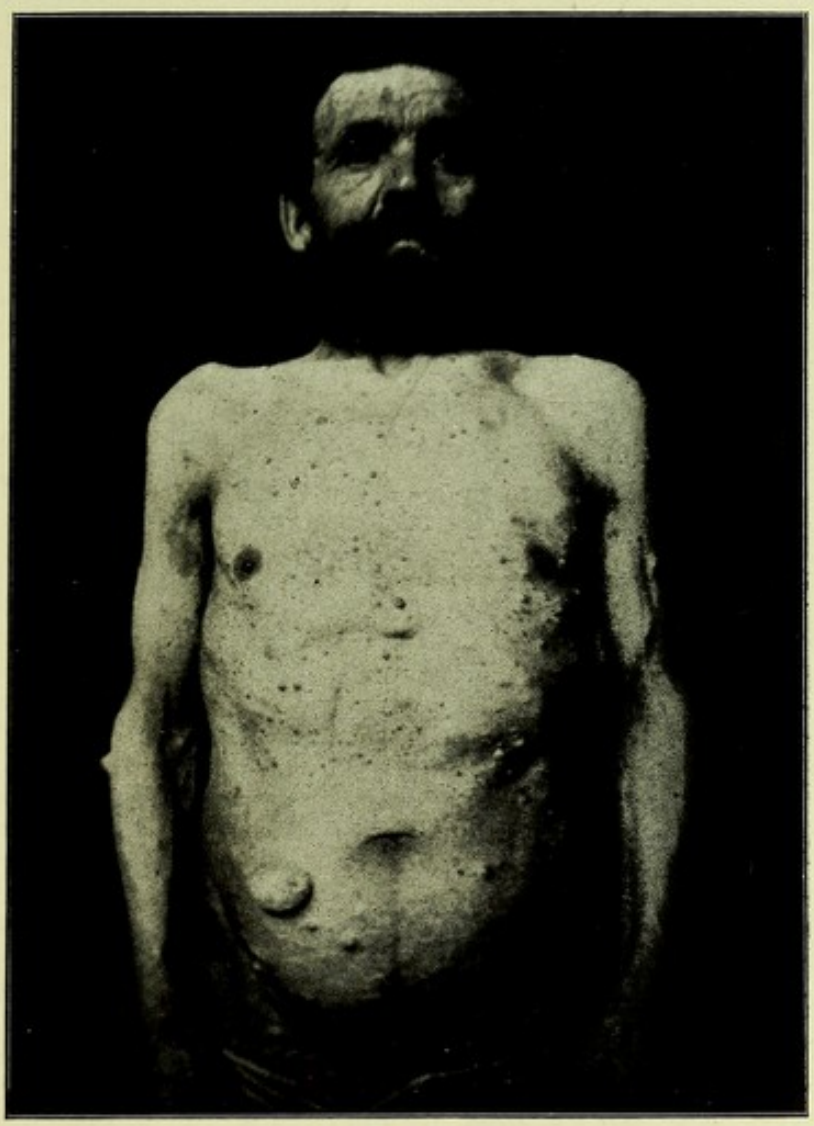

Fig. 11.—Patient 5.

tremities had existed in the four previous generations of the patient's family, often in several members of the same generation. The tendency to this condition was apparently chiefly transmitted through the female members of the family, the other cases having occurred in (1) the mother and mother's brother; (2) the maternal grandmother and her brother and sister; (3) two sisters of her great-grandmother; (4) the maternal grandfather of mother's mother. The family could not be traced farther back. For particulars see genealogical tree.

GENEALOGICAL TREE OF A. L. (CASE 9). ELEPHANTIASIS NEUROMATOSA CONGENITA IN FIVE GENERATIONS. THE MEMBERS ITALICIZED ARE THOSE AFFLICTED.

Male, A. L.'s maternal grandmother's maternal grandfather.

1. Female (normal). 2. *Female.* 3. *Female.*

1. *Female*, (?) grandmother of A. L. 2. 3. 4. *Female.* 5. 6. 7. *Male.* 8.

1. *Female* (A. L.'s mother). 2. Female. 3. *Male.** 4. Female. 5. Female.

1. *Female* (A. L.). 2. 3. 4. 5. 6.

All healthy.

Healthy children. 3 healthy children. 3 healthy children. 4 healthy children.

* Both legs and feet greatly swollen; no tumors in the skin or elsewhere; no pigmentation.

The next two cases show complicating sarcomatous transformation:

CASE 10.—In a woman 44 years old, of healthy family, there developed at the age of 26 years a fibroma of a nerve of the thigh which was extirpated but repeatedly recurred with the gradual formation of an infiltrating sarcoma of which she finally died, cachectic, at the age of 44. She had undergone ten operations in the course of eighteen years. She also had plexiform neuromata of the nerves of one thigh, multiple, circumscribed neuromata of the subcutaneous nerves of the trunk (Figs. 22 and 23) and numerous soft fibromata and pigmented areas of the skin, chiefly of the trunk.

All the cardinal symptoms of von Recklinghausen's disease were present. Of particular interest was the development of sarcoma in connection with a plexiform neuroma of the thigh (see also the following case).

CASE 11.—A woman 32 years old (Fig. 24), from early childhood had small tumors of the trunk. Gradually there appeared numerous soft and hard fibromata of the skin, particularly of the chest and back, and numerous pigmented areas. When she was 28 years old a tumor formed in the left sciatic nerve which was removed and found to be a plexiform neuroma (Figs. 25 and 26) of a large part of the sciatic nerve with pronounced gelatinous and colloid degeneration. Repeated recurrences took place and gradually the tumor assumed the character of an infiltrating sarcoma. Finally the whole sciatic nerve was transformed into a cord 4 to 5 cm. thick (Fig. 27) which adhered to the surrounding structures. On all the branches there were bean-sized, fusiform enlargements, with pronounced myxomatous degeneration. She died soon after leaving the hospital, presumably of recurrence.

CASE 12.—In a man 38 years old, who died of ileus, there were accidental necropsy findings of numerous yellowish-brown pigmented areas of the chest, back and neck, most of which were of pin-head size, others of the size of beans, and a few oval and very large areas on the lower part of the back and on the thighs (the largest measured 2 x 5 cm.). Scattered on the trunk and arms there were numerous small soft fibromata, the overlying skin of which was white and unpigmented and partly covered with long hairs. They were most numerous on the chest and back. There was a soft, very prominent nodule of the size of a pigeon's egg on the right shoulder. There were no distinct nodules on the nerves, of which the brachial plexus, pneumogastric and sympathetic nerves were dissected out. The tumors showed the structure of a fibroma rich in cells.

CASE 13.—In a woman 55 years old who died of an abdominal tumor the necropsy revealed: 1. Soft, freely movable cutaneous and subcutaneous tumors from the size of a pea to that of a nut. 2. Numerous thickly set brownish

spots on the abdomen and both thighs of the size of hemp-seeds, alternating with pigment free areas. There was also a carcinoma of the left ovary, with secondary infiltration of the omentum and extension to the peritoneum and pleuræ. Finally, there was in the mesentery a large nodular tumor mass with extensive central necrosis and softening of large portions. Microscopically this tumor was found to consist of large, spindle-shaped cells separated by scant intercellular substance, and large irregular cells with large nuclei rich in chromatin—on the whole, a decided sarcomatous structure. On the other hand, the ovarian and omental tumors

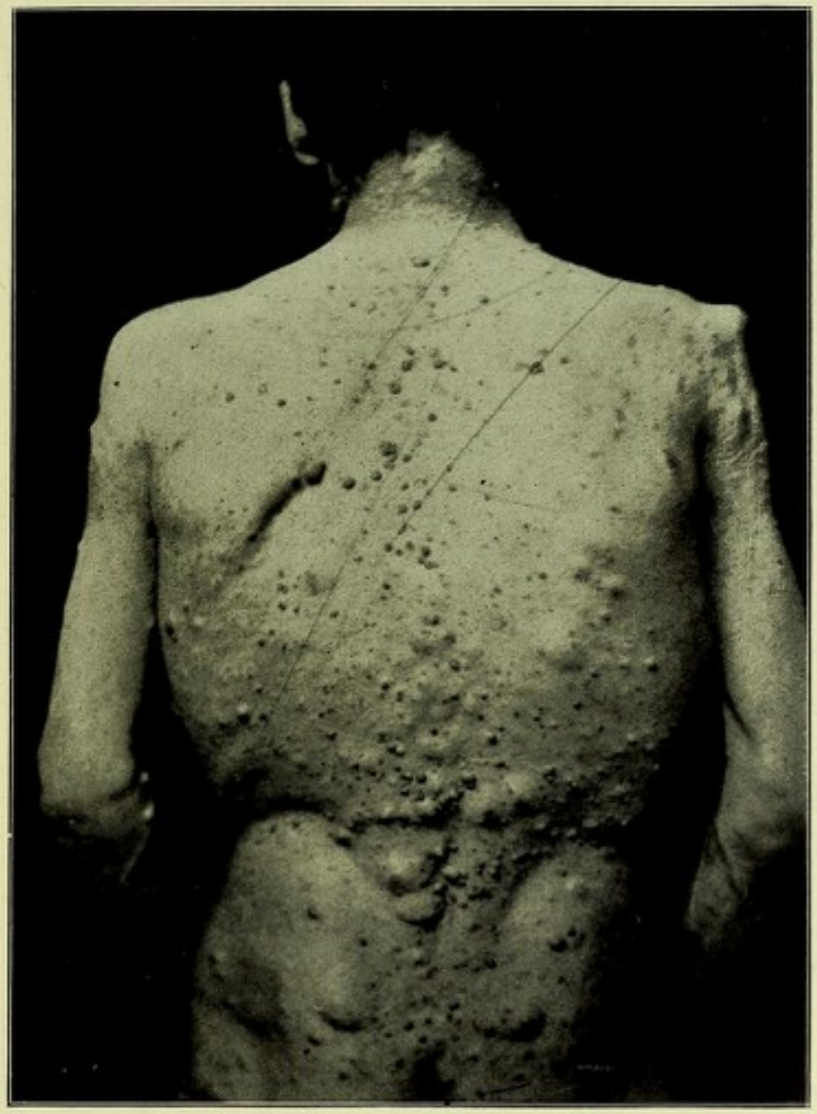

Fig. 12.—Patient 5.

showed distinct carcinomatous structure with cells of epithelial character arranged in distinct clusters, some of which possessed central lumina.

In this case we then had a combination of carcinoma, sarcoma and multiple soft fibromata of the skin.

Case 14.—An unmarried woman 51½ years old had had nodules on the trunk from birth. At the necropsy numerous nodules from the size of a bean to that of

a nutmeg were found scattered over the entire trunk, especially on the chest, and also numerous, very small, in part scarcely visible, nodules covered by soft, smooth, as a rule non-pigmented skin. The largest were located on and about the areolæ of the mammæ. On the chest there were 200 or 250 nodules, while those on the back were less numerous, but larger. On the neck there were some nodules of the size of a pea; a very few were found on the extremities. Several pigmented areas for the most part of the size of a hemp-seed, but also a few large ones, were present on the skin, especially that of the abdomen. She had also suffered for about fifteen years from a chronic disease of the larynx, probably tuberculosis. About six months before the patient's death a carcinoma of the larynx and tongue developed and gradually formed a large infiltrating tumor. No changes were found in the central nervous system, spinal ganglia, vagi, sym-

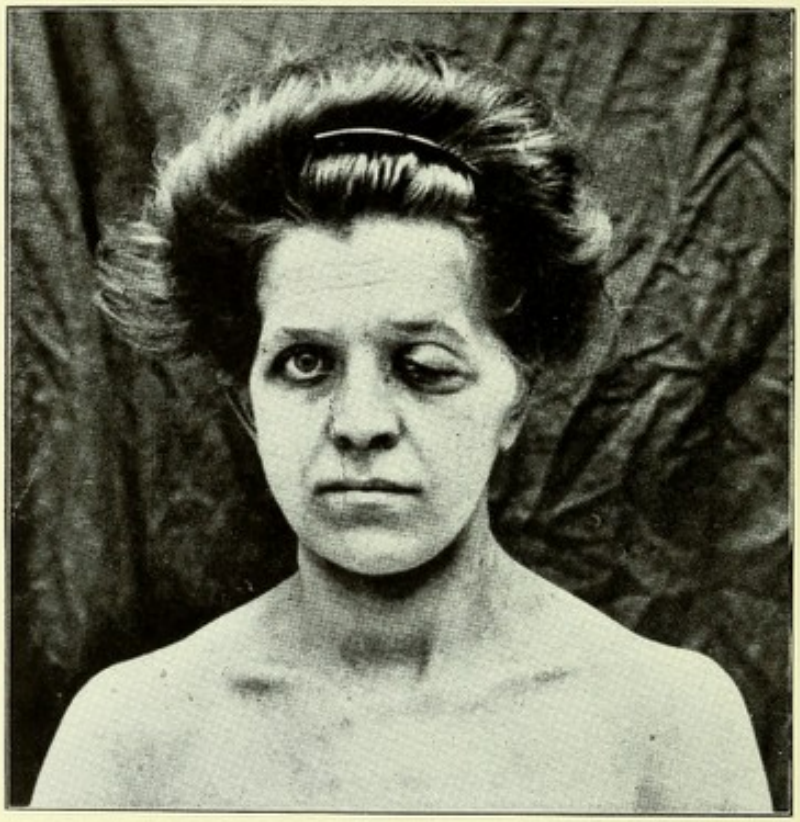

Fig. 13.—Patient 6. Plexiform neuroma in the left temple and left upper eye lid.

pathetics, cervical plexus, or sciatic nerves and their branches. There was no demonstrable family history as far as the occurrence of tumors was concerned.

Case 15.—The following very peculiar case of "elephantiasis congenita" is included, although it is very doubtful whether we are here really dealing with an instance of von Recklinghausen's disease. It is that of a new-born infant, now an old specimen in the Museum of the Pathologic Institute of Christiania. Both parents had been healthy and had four other healthy children. This child, which was born at full term, had lived thirty-six hours. It cried and nursed well. The cause of death was a left-sided pneumonia.

The appearance of the child (Fig. 28) is very peculiar, first suggesting lepra nodosa with the facies leonina. It is of the size of a full term child, being

49 cm. long and weighing about seven pounds. On the whole, it is well proportioned, although the arms are rather long as compared to the trunk. The most conspicuous features are a peculiar thickening and numerous flat prominent nodules of the skin. The skin has the appearance of being too large, with the formation of folds, especially on the extremities. On the arms and legs there are numerous transverse wrinkles and grooves separated by thick folds of skin. This is also very pronounced on the whole head and especially on the face, which for this reason has a peculiarly gruff expression. The eyes almost disappear in deep furrows between swollen eyelids, and the nose and ears look like nodular tumor masses.

The thinnest and smoothest part of the skin is that of the trunk, but here also small nodules are seen in the form of numerous scattered, fairly well circumscribed, small infiltrations. The nodules are most thickly set on the extremities, on the legs and in the palms, where they vary from the size of a hempseed to that of a bean. The skin is also diffusely infiltrated over large areas. On incision of the nodular and thickened portions the thickening is found to be in the cutis and to measure as much as 1 cm.

The internal organs were found to be normal. Nothing was found in connection with the central or peripheral nervous systems. Microscopically, sections

Fig. 14.—Case 6.—Plexiform neuroma. The white nerves with nodules have been dissected apart.

from various parts of the infiltrated skin presented the same picture, namely, diffuse infiltration with numerous small, closely placed cells throughout the cutis and penetrating into the subcutaneous tissue. The cells are small, polygonal or round, with distinct, deeply stained nuclei and abundant cytoplasm. The border of the infiltrations is diffuse, especially in the subcutaneous tissue. Any origin from the nerves could not be demonstrated.

Epicrisis.—The histologic picture is most likely to be explained as tumor formation, resembling round-celled sarcoma or mycosis fungoides, but it also bears considerable resemblance to a granuloma.

THE ANATOMIC CHARACTER OF THE DISEASE

From the description of the cases (and from the illustrations) it will be seen that the essential symptoms of multiple neurofibromatosis are: multiple cutaneous tumors, pigment anomalies, tumors of nerves in their various forms, and elephantiasis-like formations.

The most frequent and almost constant change observed is the presence of multiple tumors of the skin, the so-called mollusca fibrosa, which were found in all of our cases, though exceedingly variable in extent and size. Sometimes they are found by the hundred or thousand (Cases 4 and 14). The size varies from the very smallest point to that of a hazelnut or hen's egg; sometimes they cause trouble by their size; ulceration may necessitate removal by operation (Case 3). They are most numerous on the trunk and particularly in places subject to mechanical pres-

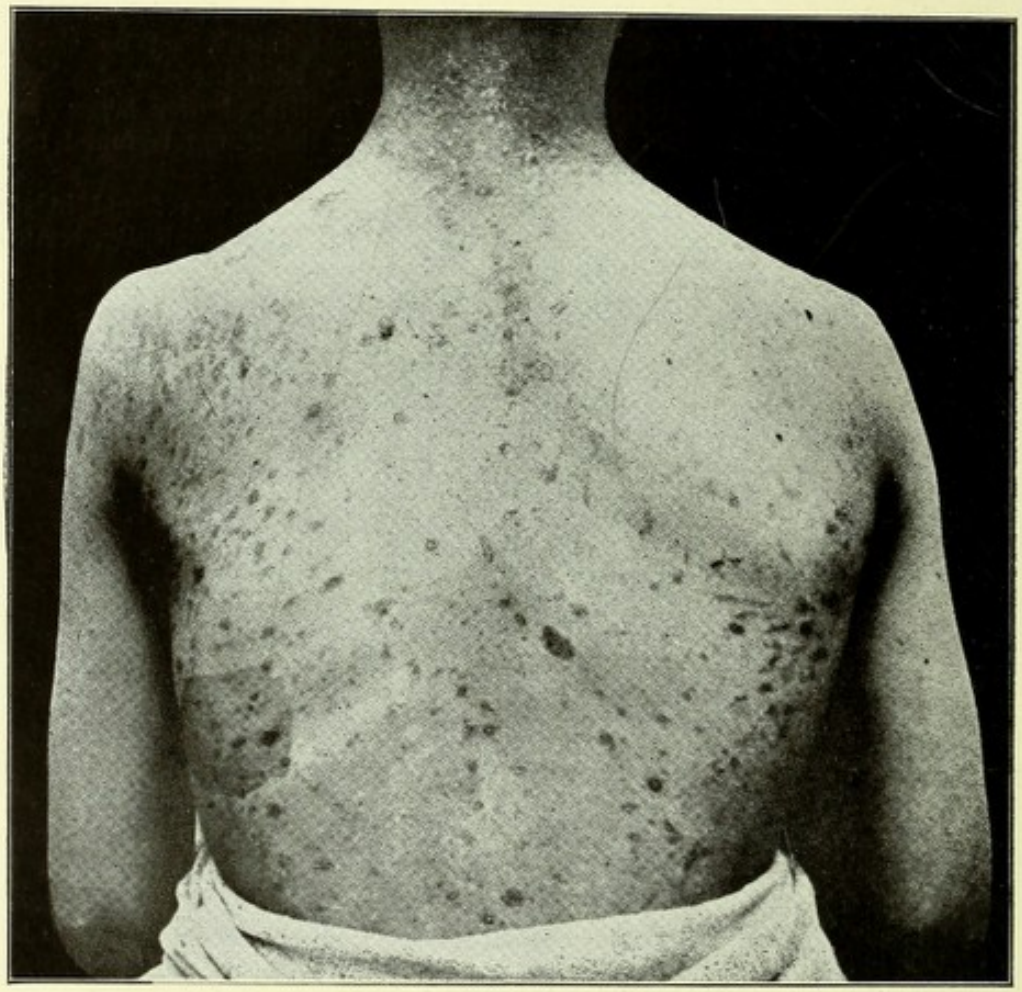

Fig. 15.—Patient 6. Pigmented and pigment-free spots.

sure—for instance, about the waist. They are also relatively frequent on the neck, head and hips, but less so on the extremities. They are generally soft, freely movable, not tender, and are partly located on the skin, partly in the deep portion of the cutis or in the subcutaneous connective tissue. When they are recent and in active growth they often appear as bluish-red or violet flat nodules or indistinct infiltrations in the skin, consisting of soft, edematous connective tissue poor in cells; later, when

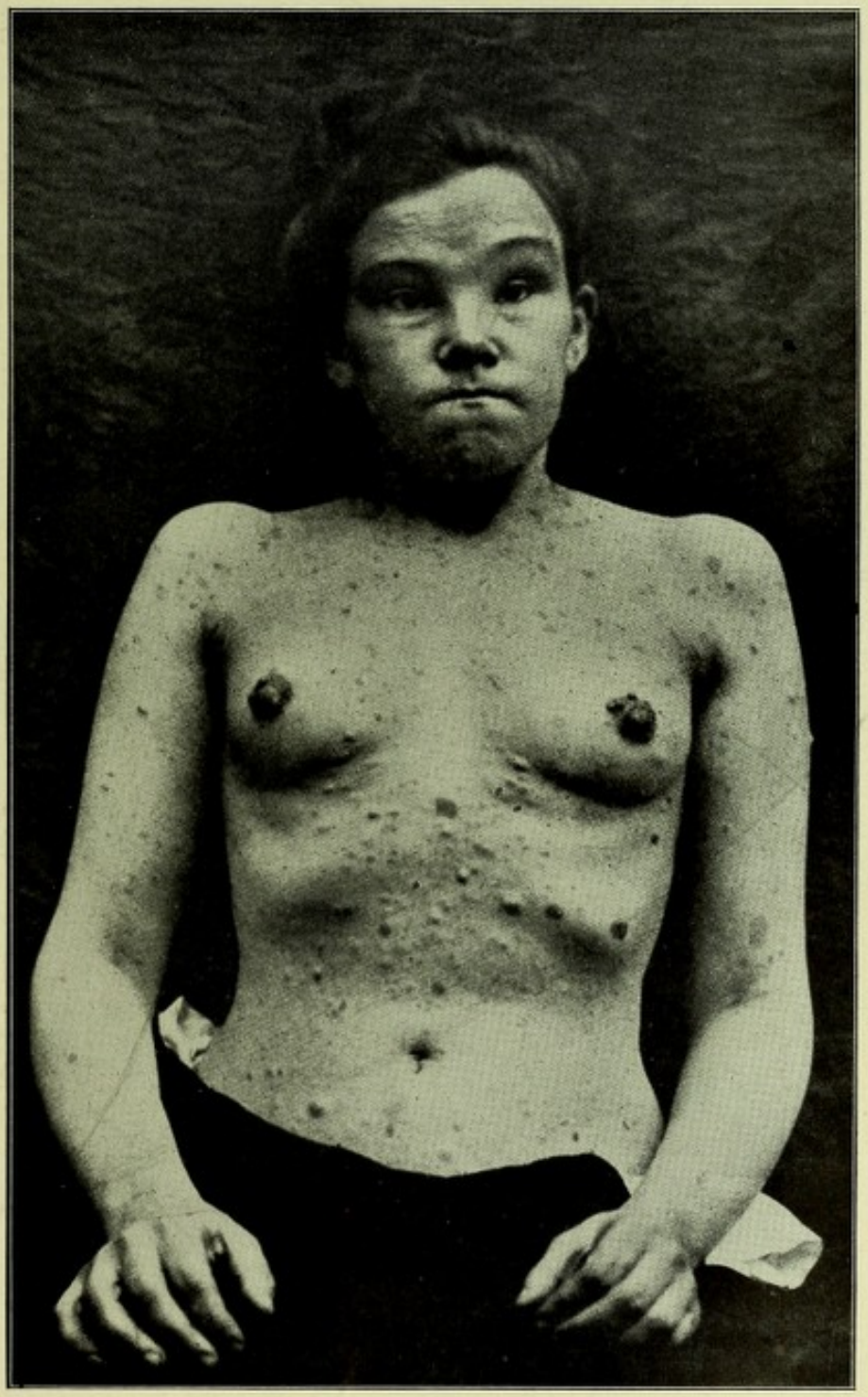

Fig. 16.—Patient 7.

fully developed, this connective tissue is often rather rich in cells. As a rule these tumors are very irregularly distributed over the skin and show no distribution corresponding to that of nerves.

At the same time one also sometimes finds tumors in the larger branches of nerves located in the subcutaneous tissue and deeper (for

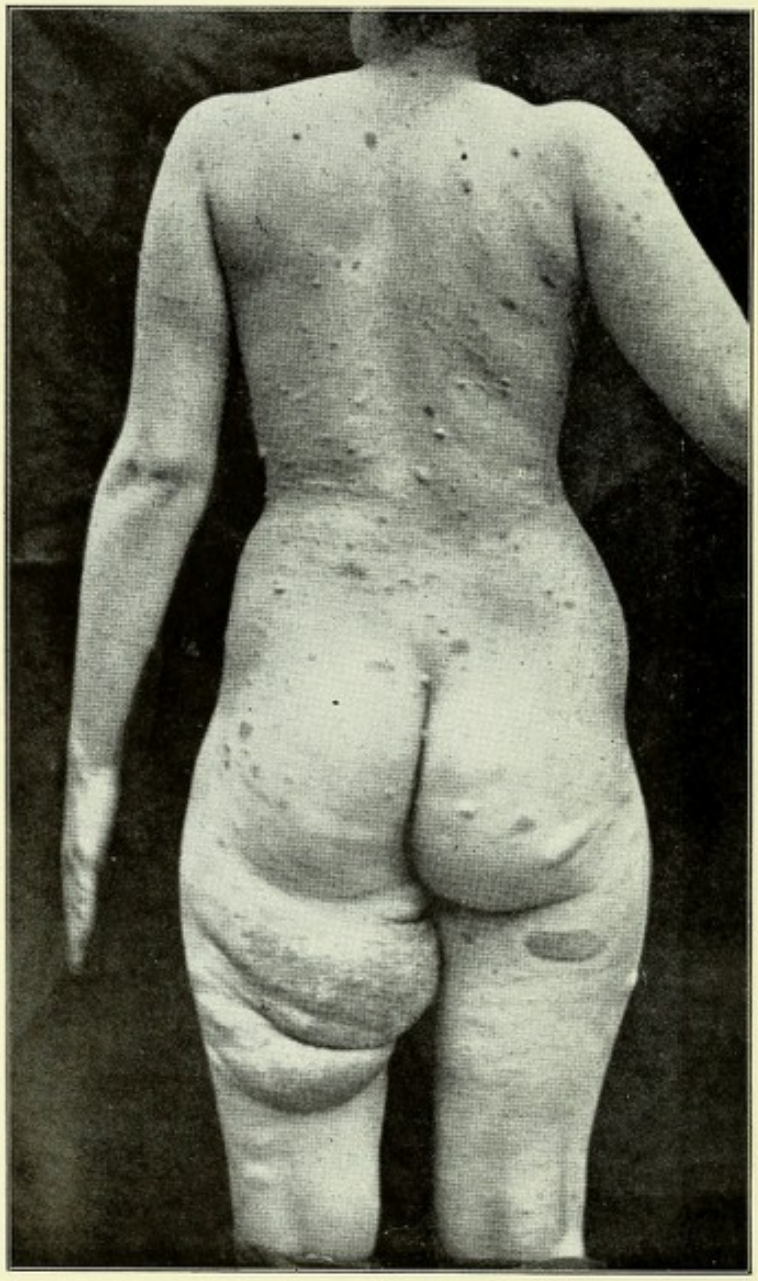

Fig. 17.—Patient 7.

instance, Cases 4, 6, 10 and Fig. 22). They are most frequently found in the nerves of the extremities, as, for instance, on branches of the ulnar, median or sciatic, but are also seen on the intercostal, pneumogastric, sympathetic and other nerves. They are generally somewhat tender so

that pressure produces radiating pains. They are spindle-shaped, movable from side to side, but as a rule not from above downward. They generally cause trouble only by their location and size. Curiously enough functional disturbances are comparatively rare, especially motor phenomena; occasionally, however, sensory disturbances are encountered.

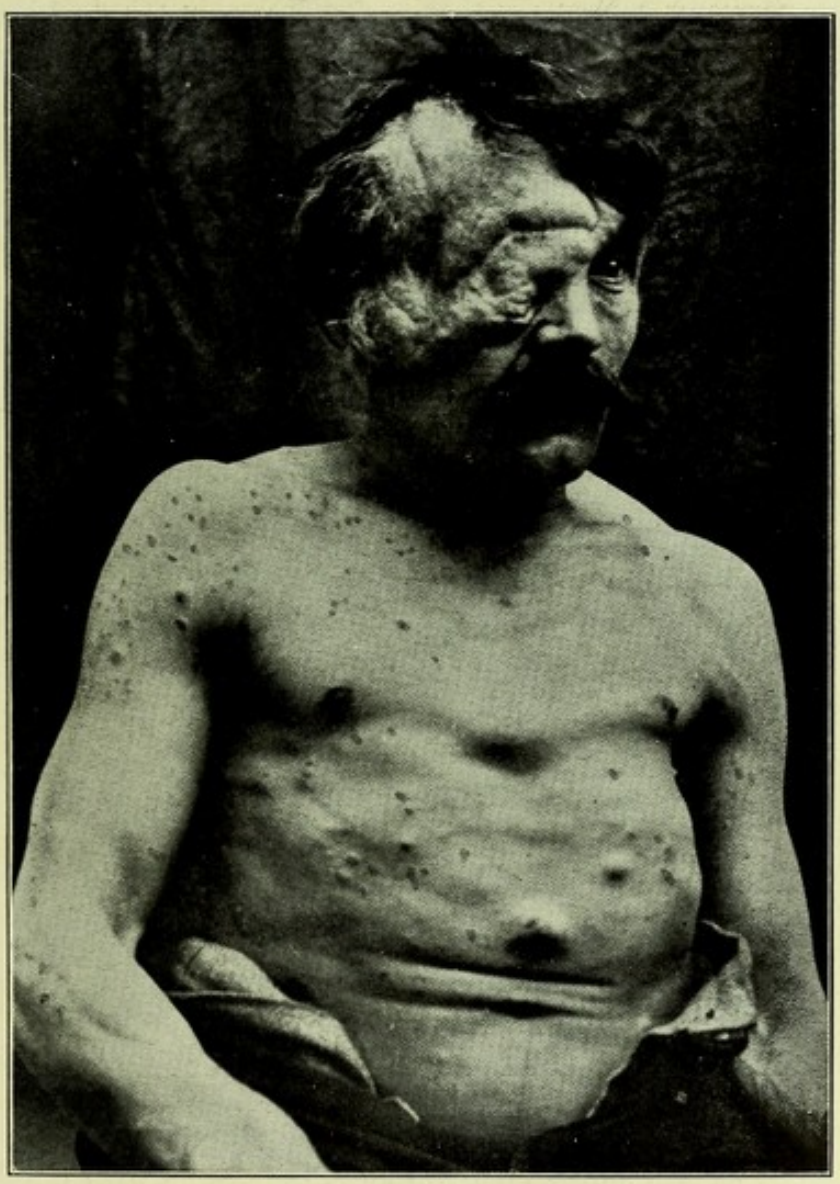

Fig. 18.—Patient 8.

The rarity of these disturbances is due to the fact that the nerve fibers in the tumors persist a long time without degenerating. If they are removed, functional disturbance is as a rule absent, possibly because other nerves have taken up their function.

But the tumor infiltration of the nerves may also show itself in different forms, namely: as diffuse infiltration, diffuse fibromatosis of one or several nerves or of a nerve plexus. The infiltrated nerves then appear as swollen, cylindrical or nodular, tortuous and branching cords, grayish-white in color and as a rule firm in consistency. This condition is spoken of as plexiform neuroma (Figs. 25, 26 and 27), especially where connection with nerves or a plexus is readily demonstrable (Cases 10 and 11). A bundle of racemose nodular masses which form a more isolated tumor

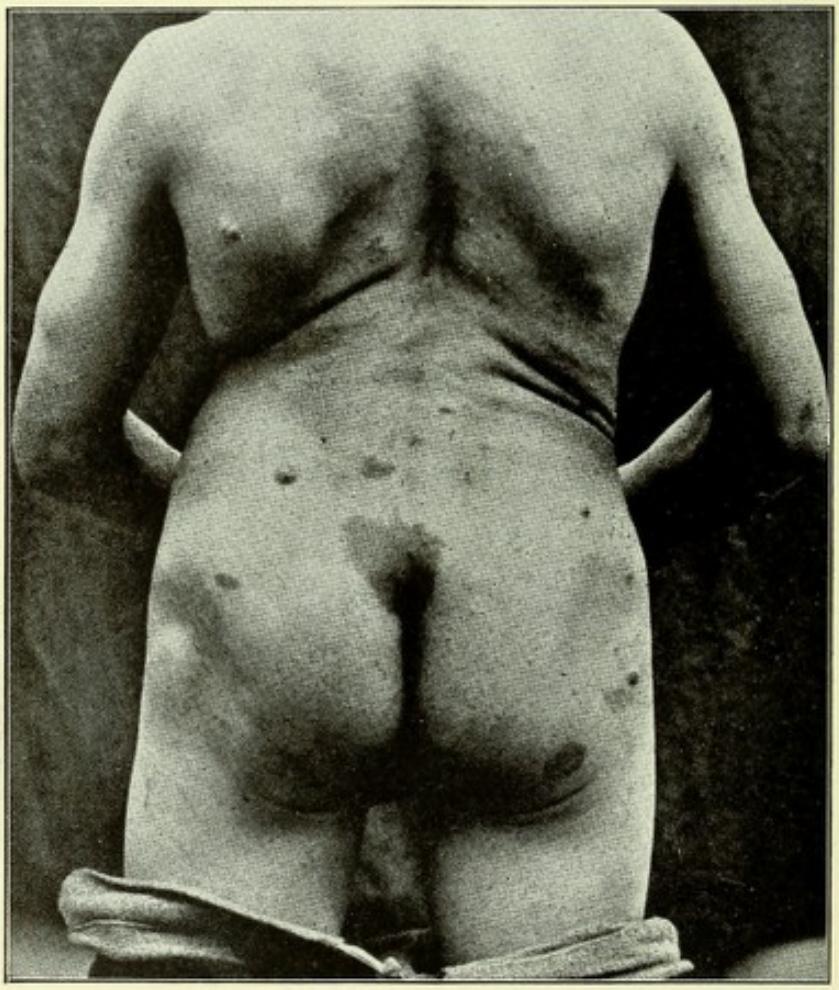

Fig. 19.—Patient 8.

with a single pedicle and without intimate connection with nerve trunks or a plexus we designate racemose neuroma or "Rankenneurom" (von Bruns) (Figs. 13 and 14). The extension here chiefly occurs in width and thickness. This form of tumor has certain favorite locations, such as the orbit and eyelids (Case 6), more frequently the upper lid (43 out of 79 cases), the temples, the region of the ears (12 out of 79 cases), the back of the neck and occiput—in general the locations which are the

favorite seats of certain forms of elephantiasis. The ordinary plexiform neuromata have other frequent locations, such as the nerves of the extremities, particularly the sciatic nerve and its branches, the vagi, sympathetics, etc.

The nerves sometimes are greatly swollen (Case 11) with simultaneous mucoid or colloid degeneration and form thick branching cords up to 1 cm. in thickness, or rather tubular formations with mucoid, thin contents (Figs. 25 and 27). In such cases it is not rare for secondary sarcomatous tumors to develop.

Strangely enough pathologic changes in the central nervous system are rarely found in association with these tumors of the nerves.

A peculiar and very interesting form of von Recklinghausen's disease is constituted by the elephantiasis-like conditions occasionally met with,

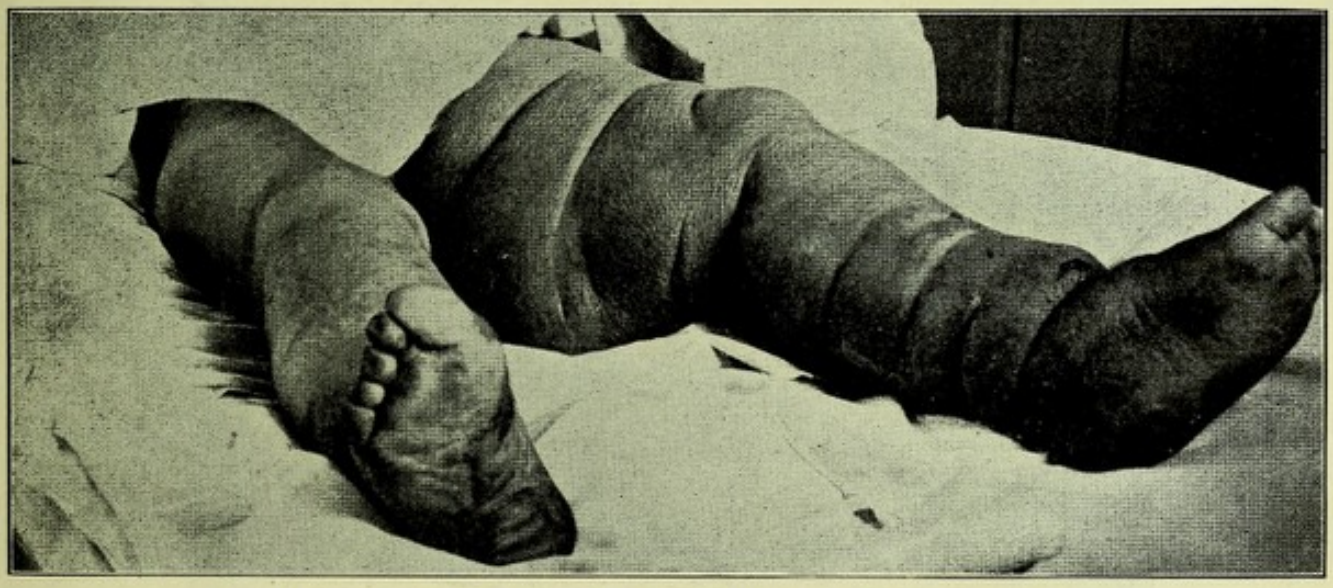

Fig. 20.—Patient 9. Congenital elephantiasis of left lower extremity.

the so-called elephantiasis neuromatosa (or pachydermatocele). This may depend upon a racemose neuroma (*Rankenneurom*) or a large tumor in the skin or a nerve being covered by thickened skin; or we may find a more diffuse thickening of the skin and underlying parts of so great an extent that real deformities result, for instance, elephantiasis of the feet (Figs. 20 and 21). The latter form constitutes the true elephantiasis neuromatosa. The most frequent locations are the feet, legs, hips, external genitals, neck and face. As excellent examples we have Case 7, elephantiasis of the thigh; Case 8, of the face; and especially Case 9, with involvement of a whole lower extremity with pronounced hereditary tendency (elephantiasis in five generations). This form is generally con-

genital, or at least appears in early childhood, and usually has a very slow, painless evolution. The skin over such thickened portions is generally hard, uneven, rough (like shagreen), often arranged in folds like a ruff or ruche. At the same time we often find multiple tumors of the

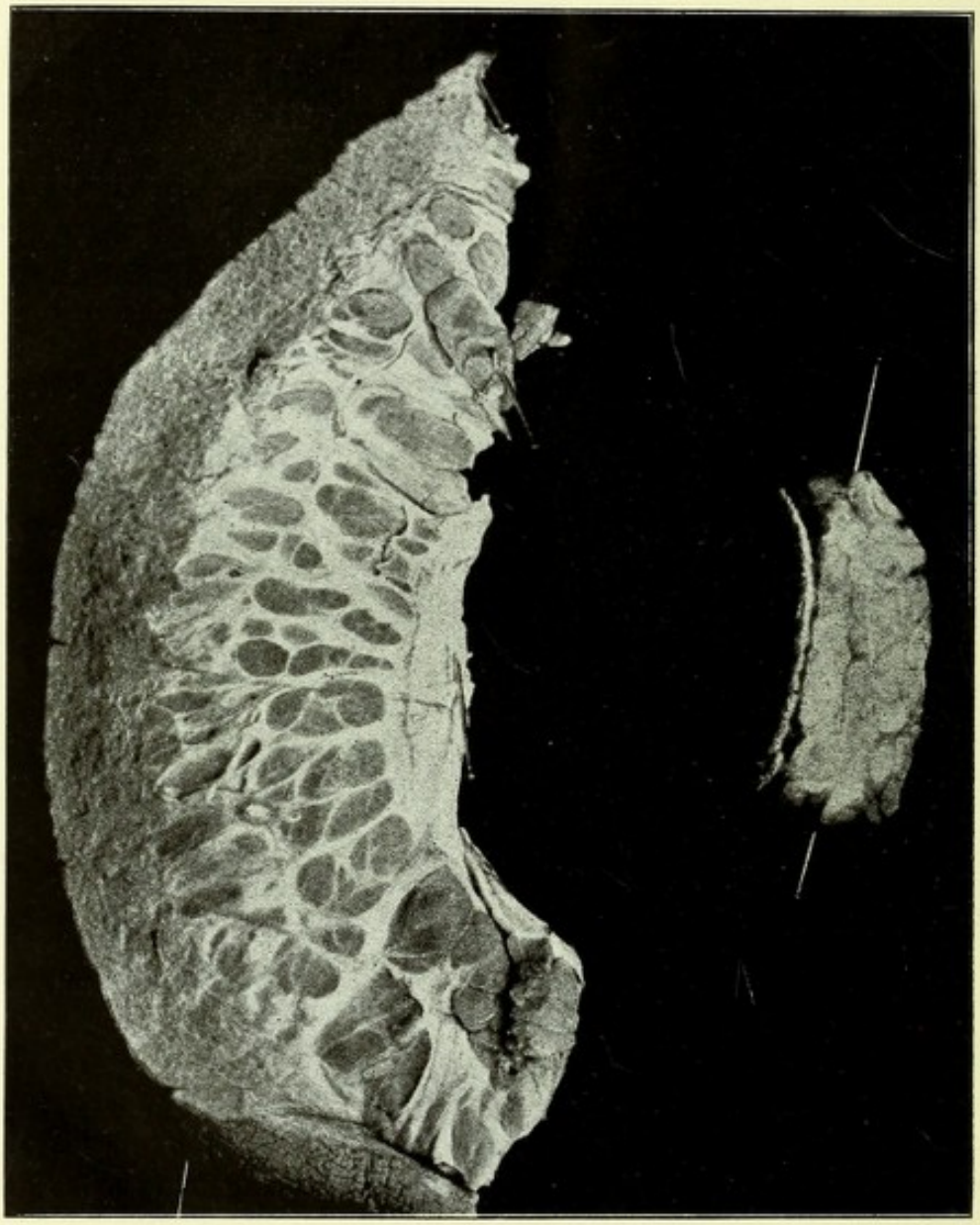

Fig. 21.—To the left. Cross-section through the thickened skin on the left leg of Patient 9, natural size; to the right for comparison, cross-section through normal skin.

skin and nerves and pigment anomalies. Case 15 is included as an "elephantiasis-like" case, a counterpart of which I have not discovered in the literature. It is, however, very doubtful what we here have before

us. The thickening of the skin did not show any fibromatous structure and no connection was to be made out with thickened and infiltrated nerve trunks.

Another pathologic finding frequently encountered in multiple neurofibromatosis is abnormal pigmentation. It is generally said to be present in 25 per cent. of all cases. This figure does not correspond with our experience, as pigment anomalies were found in all of our cases. At any rate they form a characteristic feature of the whole disease, not a mere coincidence. The pigmentation may be congenital (Cases 4 and 7) in the form of scattered small brown spots or nævi, or the discoloration is more diffuse. Frequently, however, the spots develop later in life and increase in number, size and intensity of color. They may be punctate, freckle-like and then they are often exceedingly numerous; or the pig-

Fig. 22.—Plexiform fibroma of nerve (Case 10), natural size.

ment may collect in large areas or more circumscribed patches which are then generally of a lighter, chocolate color. The shape is most frequently oval, but may be exceedingly irregular. It is very rare to observe a localization corresponding to the distribution of certain nerves or a metameric distribution. It was not found in any of our cases. In the absence of pigmented areas the skin is often found to be very dark with a diffuse brownish pigmentation. The pigmented spots are also most abundant on the trunk, neck and face, but there is no demonstrable direct connection between the spots and the tumors of skin or nerves.

Sometimes spots or patches free from pigment are seen to alternate with the pigmented ones. Occasionally one also finds angiomata of the

skin (Case 2), and this is sufficiently frequent not to be considered mere accident but a true feature of the disease. It should be remembered that certain forms of angioma, especially the so-called angioma arteriale racemosum, are frequently found together with pigmented nævi, or diffusely pigmented skin showing fibromatous thickening. It is more doubtful to what extent the rare cases of congenital multiple nodular angiomata are connected with or related to von Recklinghausen's disease. In a rare case of this sort in a 7-year-old boy with multiple tumors of the left hand

Fig. 23.—Cross-section through a small subcutaneous "neurofibroma" (microphotograph); just below the center, cross-section of a nearly normal nerve bundle; in the upper part, cross-section through a nerve bundle in which the fibers are forced apart by the proliferation endoneurium from which the tumor originates.

and forearm whom I had occasion to examine a few years ago there were none of the cardinal symptoms of von Recklinghausen's disease.

It must be stated that all the phenomena described are not always found together. Most constant according to our experience are the fibromata and pigmented spots of the skin, while the tumors of larger nerves are less frequent. The elephantiasis-like conditions are still more uncom-

mon. As to other necropsy findings, the organs are usually found to be normal aside from congenital malformations which are occasionally met with.

OTHER SYMPTOMS

Aside from the "cardinal symptoms" one also finds in von Recklinghausen's disease a series of other "secondary symptoms" ("of the second order"), which are less reliable, as it is difficult to prove their actual connection with this disease. Here belong a series of psychic abnormalities which are encountered with relative frequency. The subjects are often

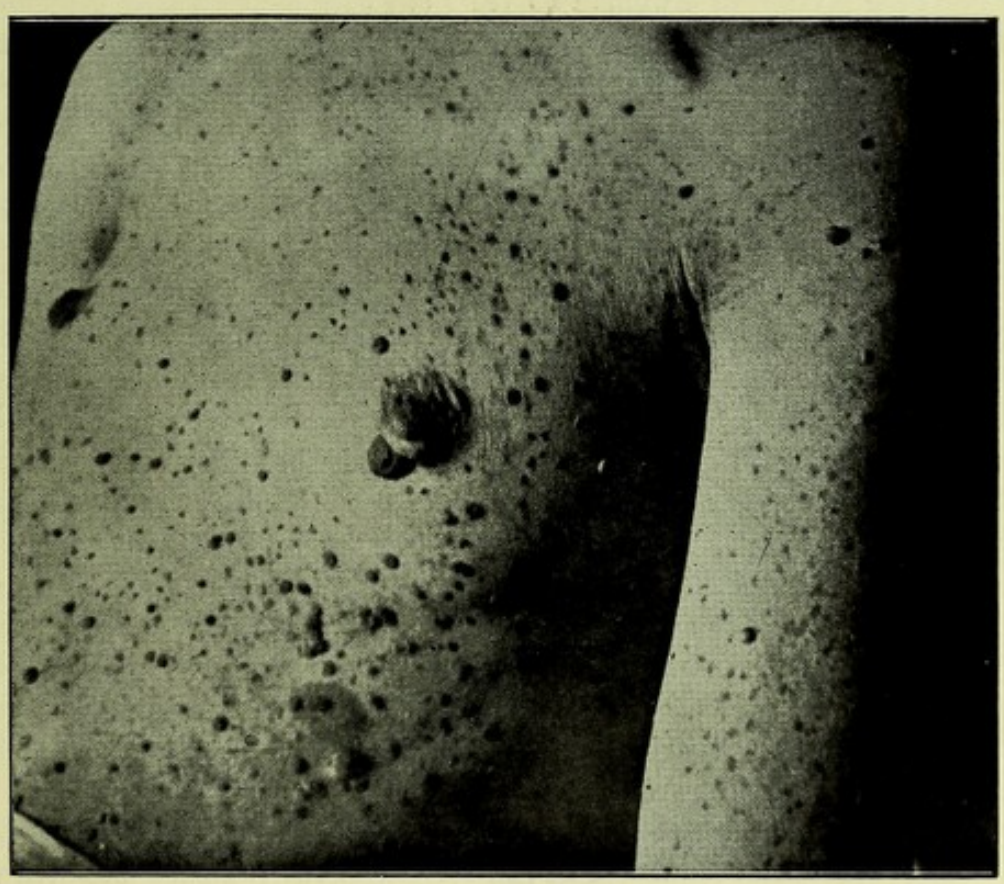

Fig. 24.—Patient 11.

dull and apathetic, of limited intelligence, or actually stupid, imbecile or idiotic. A striking example of such an imbecile of the Mongolian type is our Case 7. Congenital defects and malformations are not very rare, such as cranial defect, malformations of fingers, toes, cryptorchidism (Case 4), etc. The entire skeleton may be imperfectly developed with the appearance of nanism or cretinism. Such abnormalities are sufficiently frequent to be looked upon as symptoms of or links in the disease itself.

More doubt is attached to a series of vasomotor and trophic phenomena occasionally met with, such as certain peculiar joint affections, arthralgias and even arthritis deformans,[8] local asphyxia, peculiar attacks of unconsciousness, attacks of dizziness and cramps. Of doubtful connection are also certain osseous changes, such as a kyphoscoliosis of rapid formation (Case 8) which have been considered in connection with this disease as an expression of general cachexia, which in turn should depend on multiple neurofibromatosis (Pierre Marie, Hoisnard).

A peculiar symptom probably belonging to the disease was observed in our Case 9 (that of a woman 25 years old with elephantiasis congenita of pronounced hereditary basis), namely, for many years the regular occurrence of chills with subsequent sensation of heat and discomfort so that she was often confined to bed for one or two days at a time. Similar cases have been described by Bryk, Esmarch and Kulenkampff.

It is also of a certain interest that we not rarely meet with menstrual disturbances, either total absence or late appearance of the menses.

However, such secondary phenomena are often entirely lacking. When present they are of great interest, especially in cases in which the disease otherwise presents only one or a few of the cardinal symptoms, so-called incomplete forms or *formes frustes* which are relatively frequent and the true nature of which is more readily recognized when they occur in families in which there are pronounced cases of von Recklinghausen's disease.

ETIOLOGY AND EVOLUTION.

The disease occurs at all ages and in both sexes but apparently with greater frequency in men. According to the most extensive statistics 65 per cent. of all cases are in men. This does not correspond with our experience, as of our fourteen cases ten were in women and four in men; our figures are, however, obviously too small to admit of conclusions.

Hereditary disposition is not infrequently demonstrable on one or the other side of the family; this has been observed in about one-fifth of all cases. The disease may appear in several brothers and sisters, or it may have occurred through several generations, and not uncommonly in different forms in different generations. "La neuro-fibromatose généralisée est congenitale toujours, héréditaire souvent et quelquefois familiaire" (Feindel). Among our cases the disease was found in mother and daughter (Cases 1 and 2). Particularly interesting is Case 9 with

8. In the interesting case of Hektoen and Preble (Am. Jour. Med. Sc., 1901, cxxi, 1) there were, in addition to multiple tumors of cerebrospinal and sympathetic nerves, a polyarthritis deformans, kyphoscoliosis with ankyloses and contractures, and decubitus (mal perforans) and gangrene of one foot.

congenital elephantiasis in five generations, a unique or at least extremely rare observation. Nonne[9] has reported elephantiasis of the feet in eight members of the same family in three generations.

The disease, or at least some of its symptoms, may be congenital. This is particularly true of cases of elephantiasis (Cases 8 and 9). Tumors of the skin have also been observed from birth (Cases 11 and 14) but more often appear later. Congenital tumors of the nerves—multiple or isolated—have not been observed as far as known, although it certainly may be taken for granted that they have a congenital *anlage*. They sometimes are discovered in childhood (Case 6 and Case B), more often at the age of puberty, but also frequently at the ages of 40, 50 or 60, when prolonged latency must be assumed, as the tendency is congenital. As has been stated, the pigmentations may be congenital.

The evolution of the disease varies, but as a rule it is very slow, requiring many years. Most patients die with the disease, not from it. Ordinarily tumors and pigment spots in the skin begin to appear in small numbers; later new eruptions occur, often separated by intervals; at a more advanced stage tumors in nerve trunks and large cutaneous tumors appear. At a mature age the picture is usually very pronounced with numerous large tumors and extensive pigmentation. This is illustrated in our Cases 1, 2, 3, 4 and 6. The eruption of new nodules and pigmented areas is sometimes, though rarely, arrested. On the other hand, the fibromata of nerves often cease to grow after having broken out in large numbers, and sometimes even after repeated recurrences after operations new nodules cease to appear, the disease having become stationary (see the two cases, A and B, described in the beginning of this article). A large elephantiasis-like growth may develop slowly and steadily for years, then cease growing and become stationary (Case 8).

External influences appear as a rule to exert little influence, though in certain cases the disease seems to have a predilection for places where traumatic insults may be operative. It has also been thought that cold and moisture may call forth new eruptions or hasten their development; likewise chronic irritative conditions of the skin, bad hygienic conditions, mental suffering; all this, however, is very uncertain. But there is reliable evidence that intercurrent infectious diseases and intoxications may have such influence. Experience has shown more rapid progress of the disease especially during certain physiologic periods, such as puberty, menopause, pregnancy, puerperium, lactation (see Case 6).

Of great practical importance is the malignant metamorphosis of the tumors and especially the influence of surgical intervention in the course

9. Nonne: Virchow's Arch. f. path. Anat. [etc.] Berl., cxxv.

of the disease. In this respect the different forms behave very differently, an important fact to know both in connection with prognosis and treatment. Removal of the ordinary soft fibromata only comes into consideration when they cause annoyance by their location or size; they are readily removed and do not tend to recur. The same is true of the ordinary slowly developing forms of elephantiasis, which as a rule do not recur. The racemose neuromata (*Rankenneuromen*) also develop rather slowly

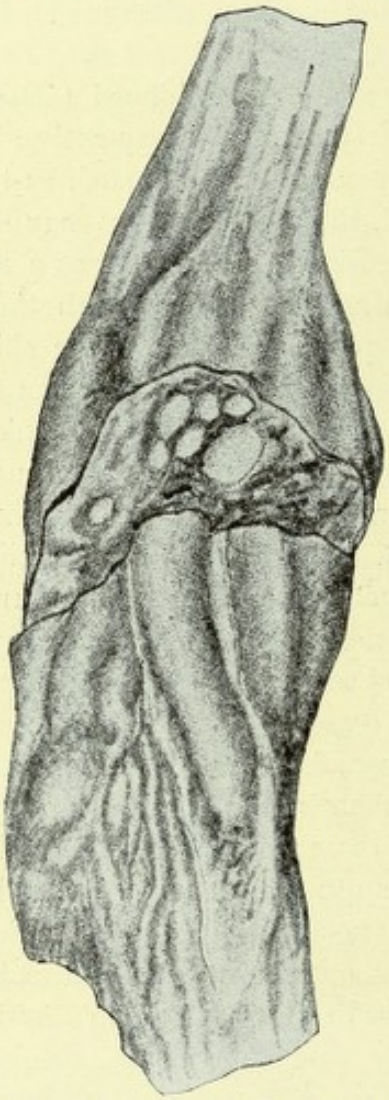

Fig. 25.—Drawing of a part of the plexiform neuroma of the sciatic nerve (Case 11). Here the tumor consists of a bundle of greatly thickened nerve fibers infiltrated with tumor tissue and matted together. On the cut surface are some of the thickened fibers that have undergone myxomatous and colloid degeneration.

and have a good prognosis; operative intervention does not seem to have an unfavorable influence on them. Our Case 6, however, seems doubtful in this respect.

The multiple deep-seated fibromata of nerves are also often removed with permanent cure, but in other cases rapid recurrence takes place. Even then, however, experience has shown that the disease may finally be arrested without further recurrence and without development into sarcoma (our first two cases, A and B, are good examples), but sarcomata have been known to develop, though slowly and after the elapse of many years (Case 10). Most caution as to prognosis is necessary in the case of ordinary plexiform neuromata, as development into sarcoma here is

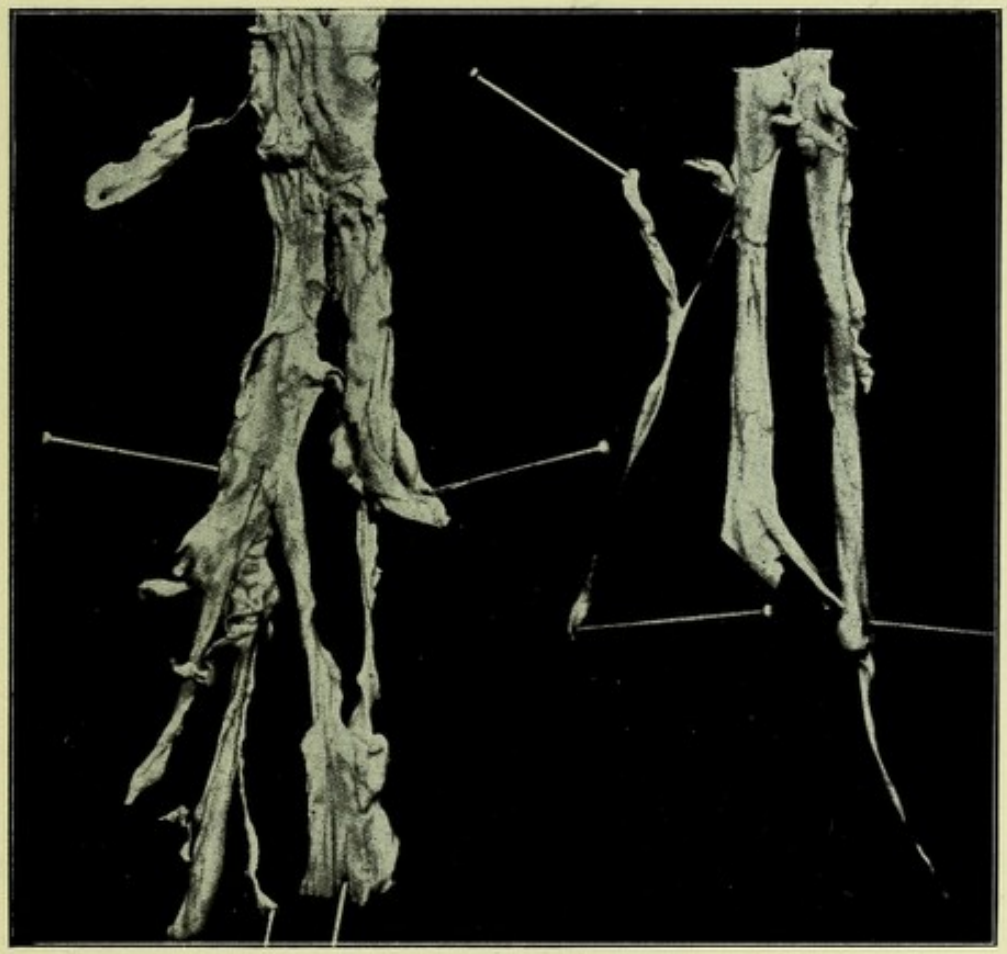

Fig. 26.—Plexiform neuroma in the sciatic nerve and its branches (Case 11).

not rare and sometimes operative intervention apparently hastens this development (see Cases 10 and 11), which has been given the undesirable name of "malignant degeneration;" the result is a rapidly growing infiltrating sarcoma. In many such cases it can not be denied that extirpation has had an injurious influence. There is rapid recurrence at the site of operation or diffuse eruption of nodules over large portions of the nerve plexus. Caution, therefore, is advisable in attacking these tumors

surgically, and if operation be performed the nerves affected should be extirpated to the greatest possible extent; in the case of sarcoma amputation ought to be performed (Thomson). Such evolution in the direction of malignancy is not rare. If all forms are considered it occurs in about 12.5 per cent. of the cases.

It is an interesting fact in connection with these growths that the simultaneous occurrence of other tumors is not unusual; such tumors may be benign or, more commonly, malignant, carcinomata or sarcomata, of external or internal organs. Our Cases 13 and 14 are good illustrations of this, Case 13 being especially noteworthy on account of the existence of both sarcoma and carcinoma. The relationship of these tumors at present is inexplicable, but their coexistence in these cases can not be looked upon as mere coincidence, and it appears justifiable to assume a

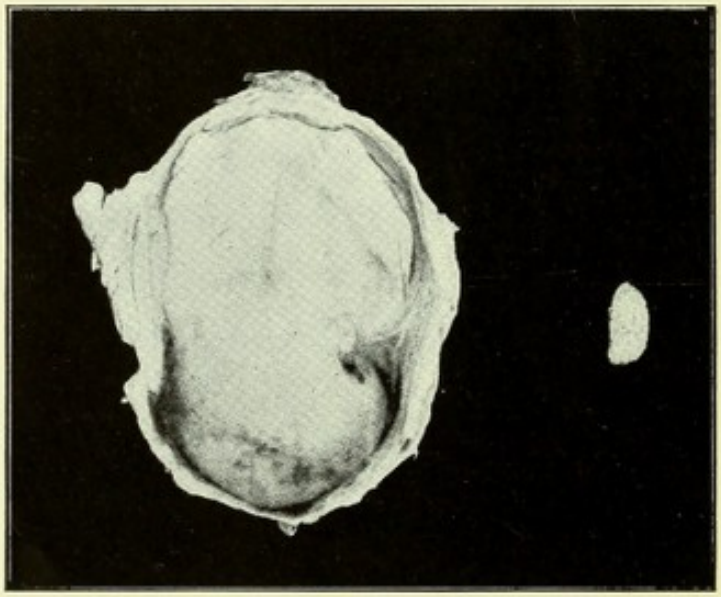

Fig. 27.—Plexiform neuroma in the sciatic nerve (Case 11). Cross-section through a greatly thickened and infiltrated nerve (to the left); to the right, cross-section of a normal sciatic nerve for comparison.

common disposition to formation of different growths. In this connection one is also naturally reminded of recent cancer experimentation in which, for instance, on transplantation of mouse carcinoma a sarcoma gradually may be evolved.

Is spontaneous recovery possible in multiple neurofibromatosis? Definite instances are scarcely known. It is not rare, however, for some nodules to disappear spontaneously, though it is hardly probable that subsidence of all the phenomena of the disease has been observed. That the disease may become stationary is an entirely different matter.

I do, however, know of one case of probable multiple neurofibromatosis (occurring in Christiania) in which spontaneous recovery has, apparently, taken place. A man of 70 years, still living, between the ages of 30 and 35 had several eruptions of cutaneous nodules on the arms, legs and shoulders. The nodules were soft, not tender, of pea to walnut size, and were thought to have been multiple sarcomata, a diagnosis which had been confirmed by four professors of medicine who successively examined the patient. An extirpated nodule was said to have shown sarcomatous structure and an unfavorable prognosis was made. The patient went to Kreuznach in two successive years to take the baths, and to the surprise of himself and his physicians all the nodules gradually and completely disappeared. When I examined him in February, 1908, there were no nodules to be found in the skin or nerve trunks, but there were several pigmented areas in the skin, some of which were rather large. The exact nature of this case can not be definitely determined, but it does not seem improbable that the nodules were neurofibromata of the skin and nerves.

PATHOLOGIC HISTOLOGY

Extensive microscopic examination of extirpated nodules of skin and nerves and pigment areas has been made in nearly all cases described, and on several occasions in cases where repeated operations had to be performed. In this way it has been confirmed that the tumors of the skin develop from the small cutaneous nerves and not from the connective tissue surrounding glands, vessels, etc., as has been supposed, among others by von Recklinghausen. It has further been found (Cases 10 and 13) that the tumors both of the cutaneous and larger subcutaneous nerves arise from the connective tissue portions of the nerves, their endo- and perineurium, and thus are to be looked upon as typical fibromata—which is in accord with general opinion. Most of the tumors are sufficiently characteristic to be recognized as fibromata, but not infrequently there is such abundance of cells that one may be in doubt as to whether the tumors may not be atypical and malignant; there are some cases in which it is very difficult, from the structure of the tumors alone, to form a conclusion as to their nature. The decidedly atypical tumors appear like ordinary spindle-celled sarcoma (sometimes giant-celled sarcoma), but transitional forms which are encountered in the case of slowly growing and recurring tumors are very difficult to interpret. The transition into malignant tumors also is as a rule very gradual, and the histologic pictures correspond to this; hence these growths also illustrate the fact that no sharp line can be drawn between benign and malignant, typical and atypical tumors.

The question has been raised whether these tumors of nerves could possibly be due to a proliferation of the sheaths of Schwann, the cells of which are now generally supposed to arise from neuroblasts and to be of

Fig. 28.—Subject in Case 15.

ectodermal origin. In this case the tumors would be more nearly related to gliomata. No evidence has, however, been produced in favor of this view, such as the occurrence of larger, more homogenous, embryonal cells,

signs of abundant nuclear proliferation, syncytial bands analogous to those seen in regeneration of nerve fibers or intracellular differentiation with formation of nerve fibers. Nothing of this kind is found. We see only ordinary fibrous tissue with intercellular substance, and it is scarcely probable that the cells of the sheath of Schwann, if they really are neuroblasts, should be able to produce ordinary connective tissue. It, therefore, appears incorrect to regard this disease as ectodermal, as do some French authors.

The racemose neuromata (*Rankenneuromen*) and the ordinary plexiform neuromata have the same evolution. In the cases of elephantiasis described it was also possible with more or less certainty to prove the origin of the thickening from the connective tissue of the nerves, but no proliferation of the connective tissue of vessels or cutaneous glands was found.

As to the nature of the disease, it must be looked on as a congenital anomaly, a form of malformation in the widest sense of the word, which has affected more or less extensive parts of the nervous system and also expresses itself in symptoms on the part of other portions of the organism or even in the entire constitutional makeup. This conception is based on various grounds: (1) the fact that the disease or some of its most prominent features may be congenital or at least arise in early childhood; (2) that the disease often develops on a pronounced hereditary basis; (3) that the tumors show a primary multiplicity, which experience has shown to be a sign of congenital anomaly; (4) that the disease is not infrequently combined with congenital anomalies and malformations of various kinds. But it is often true that the congenital disposition remains latent for a long time and then, on account of various etiologic factors, calls forth tumors of skin and nerves. In what this congenital anomaly of the nervous system consists we know nothing, but we must assume that it is situated in and affects the connective tissue parts of the nerves. That the development of the tumors, as has been supposed, should be directly due to an influence exerted by the central nervous system is without foundation, and is, in itself, highly improbable, nor does the distribution and localization of the cutaneous tumors and pigmented areas support such a hypothesis. The pigment anomalies, as constituting an important and very frequent symptom, must be considered part of the whole clinical picture. Histologically the pigment in the skin was similar to that in all other accumulations of pigment, and I have not succeeded in establishing a connection between these pigment

anomalies and pathologic conditions, tumors or other changes of the corresponding nerves. It appears reasonable at present, therefore, to look on the abnormal pigmentations as expressions of the same congenital disposition which has coincidentally caused the development of the abnormalities of the nervous system, but their exact connection is for the present entirely in the dark.