16. NEUROFIBROMATOSIS

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This is a congenital affection characterised by pigmented spots on the skin, cutaneous fibromata, multiple neurofibromata of the cranial and peripheral nerves, and, in some cases, skeletal changes, endocrine syndromes and "heterogeneous tumour formation" of the nervous system. According to Kinnier Wilson (1940), it was first described by R. W. Smith in 1849. In 1882 the histology was discussed by von Recklinghausen whose name is still attached to the disease by many. Valuable accounts of the skeletal changes were published by Brooks and Lehman (1924) and Holt and Wright (1948), and in children by Leader and Grand (1932). In tuberous sclerosis, a rare condition possibly allied to neurofibromatosis (Weber 1924), bone lesions have also been described (Heublein et al. 1940 and Ackermann 1944).

Hereditary and familial influences are in evidence not uncommonly. It has been seen in six generations (Gardner and Turner 1940). Four brothers showing signs of the condition were reported by Garland (1941).

Age—It is seen at all ages. Since at least some skin lesions are present at birth the condition may be recognised within the first few months of life. In some cases there appears to be an exacerbation at puberty.

Sex—Males are rather more frequently affected than females.

Etiology—It is considered to be a congenital anomaly due to defective germ plasm, but the cause is entirely unknown. Trotter (1926) suggested that faulty insulation of nerve fibres was responsible.

Clinical signs—In most cases typical lesions in the skin are present and the diagnosis is obvious. The skin lesions are of two kinds, café-au-lait spots or freckles and fibromata. The pigmented spots have smooth outlines and vary in size from a pin head to a five-shilling piece, but occasionally they are much larger. They tend to increase in size and number as the child grows. The distribution varies, but in some cases this is limited to the region of the pelvis and adjacent parts of the trunk and thighs. The cutaneous fibromata (fibroma molluscum) are either flat or raised. The colour may be that of the surrounding skin or it may be pink, violet or blue. They are of all shapes and sizes from a millet seed to an orange. Some present as a fold; others are pedunculated. They are soft and may feel like a bag of worms. There may be thousands present covering the entire body. Usually they are symptomless. The fibromata of nerve trunks may be in, on, or loosely attached to the nerves. They may be confluent. Those that are subcutaneous or reasonably accessible can be readily felt. They may be painful or tender, even sufficiently tender to produce protective spasm. There may be a plexiform neuroma, pachydermatocele or elephantiasis of a limb: in each of these conditions a bone in the vicinity not uncommonly shows radiographic changes. The nervous syndromes met with naturally vary with the locality of the fibromata. Tumours of cranial and spinal nerves, or of the cord or brain, give rise to a variety of symptoms, even to a sensori-motor paraplegia.

As in other conditions, the syndrome may be incomplete, the lesions being confined to the skin, or to the nerves, or they may be entirely central.

The skeletal affections are of two kinds—scoliosis and changes in the bones. Scoliosis is by far the commoner, occurring in about half of the cases. The part most commonly affected primarily is the lower dorsal region, but it may begin in the cervical. It is often associated
with some kyphosis, and is definitely progressive. Pain may be a troublesome feature. In advanced cases the rotation of the vertebrae is marked, and the curves are very abrupt. Paraplegia has actually resulted from the severity of the deformity alone (Miller 1936).

Changes in the bones, said to occur in 7 per cent. of the cases (Reuben 1934), are usually free from symptoms. Skin and bone lesions may be superimposed. They may be associated with either diminution or accentuation of growth of a bone: the latter is more common and is rarely seen without soft tissue changes in the neighbourhood. Only exceptionally do changes in the bone lead to a fracture and pseudarthrosis. Bowing of a tibia may precede pseudarthrosis, and the bowing may even be present at birth (Holt and Wright 1948). General asymmetry of the face, body and limbs with unilateral distribution of the bone changes was described by Friedman (1944). Cases with neurofibromata affecting the viscera have been described.

**Blood examination** gives negative results.

**Radiological appearances**—In most cases the scoliosis is unaccompanied by obvious lesions in the vertebrae. There may, however, be "cystic" changes in the bones (Capener 1935, Seddon 1935). Collapse of a body may occur. Erosion of the bodies from behind or enlargement of the intervertebral foramina may result from pressure by neurofibromata of spinal nerves. In a case published by Pugh (1930) there was an open clear wedge in the midsagittal region on the convex side of the curve, suggesting that an intervertebral space had gaping.

In other parts of the skeleton a variety of changes may be seen. A periosteal neurofibroma may cause smooth erosion of the cortex: in such a case a thin shell of bone is occasionally formed by the periosteum over the fibroma, the appearance being that of a cortical "cyst." The bone adjacent to a cortical erosion usually shows increased density which may be widespread. There may be "cystic" lesions in a long bone, but some which are apparently endosteal are really cortical in origin. A case with a large smooth excavation in the left ilium and complete disappearance of the horizontal ramus of the right pubis was reported by Heublein et al. (1940). Curious multiple cystic changes in the metaphyses of several of the long bones (the appearance being a little suggestive of dyschondroplasia), with the mandible and one vertebra also involved, were reported in an infant by Holt and Wright (1948). In another case published by these authors (a girl of four months) with less marked changes, the bone lesions disappeared completely. Increased density of the shaft of a bone may occur with no obvious erosion of the surface by an adjacent fibroma: this increased density often ends in streaks towards one end of a bone. Occasionally irregular thickening of a bone is seen. As already stated, an affected bone may be shorter or longer than its fellow. Tanner (1946) reported a case with a large neurofibromatous tumour adherent to the bones on the front of the leg, and with the tibia (but not the fibula) four and a half centimetres longer than the other and showing extensive irregular sclerotic changes in a radiograph. A somewhat similar case with the periosteum over the tibia greatly thickened was reported by Weber and Perdrau (1930). The ribs and the mandible sometimes show changes. An osteomalacic condition, particularly affecting the ribs, has been reported by Gould (1918), and multiple incomplete fractures by Brailsford (1948).

Associated with elephantiasis, two types of osseous change may be found affecting one or more of the bones—increase in both density and length and diminution of calibre without other structural change. Brooks and Lehman (1924) reported a case in which one tibia was eight centimetres longer than its fellow. In a case reported by Friedman (1944), a man aged thirty-one years with elephantiasis of one leg below the knee, there were several smooth indentations on the anterior surface of the tibia and considerable dense thickening of the bone: the affected leg was three centimetres longer than the other. The shafts of the humerus, radius and ulna were curiously slender in an arm affected by elephantiasis in one patient, and long thin metatarsals were seen in the foot of another: after amputation of this foot the fibula became attenuated (Holt and Wright 1948). In a third case published by these authors
similar changes were found in a clavicle and some ribs after removal of a supraclavicular neurofibroma. Slender bones may, however, occur without obvious changes in the soft tissues. A long thin humerus, associated with clear bulbous ends to each of the three bones forming the elbow joint, which was dislocated, was noted by Mondon and Leger (1946). In one case we found curious sharp lipping of the margins of the great trochanters and the ilia, a feature we have not seen reported by others (Fairbank 1939). The skull may show patches of either increased or decreased thickness, but these are exceptional. Increased density suggestive of leontiasis, but without thickening, we found in one case. Erosion of the occipital and petrous bones associated with a tumour of the auditory nerve was reported by Camp (1929). The pituitary fossa may be enlarged but as a rule it is normal.

**Progress**—The various types of lesion, skeletal and other, may or may not be progressive. The scoliosis, however, usually shows a tendency towards progressive increase of the curves, in spite of careful conservative treatment, and may eventually cause severe or complete crippling—an important fact to keep in mind when treatment is under consideration.

**Complications**—Paraplegia may develop in cases with severe scoliosis, even in childhood: as already mentioned it may also result when fibromata develop on spinal nerves. Complications arising from endocrine errors include acromegaly—three such cases were reported by Tucker (1924)—and hyperparathyroidism. It has been suggested that occasionally the two conditions described by von Recklinghausen, neurofibromatosis and hyperparathyroidism, are associated (Stalman 1933, Cohen and Douady 1936). Sarcoma undoubtedly develops in some cases, but the frequency is uncertain: 12 per cent. is the figure given by Hosoi (1931) and 5-5 per cent. by Holt and Wright (1948). Neurofibromatous tissue was found in a tibia adjacent to a definite sarcoma of the bone (Norley et al. 1945). Sarcomatous change may occur in more than one fibroma (Miller 1936). Neurofibromatosis, Paget's disease and sarcoma of the pelvis were associated in one case known to us, a man of fifty-three years.

Mental deficiency and syringomyelia have been reported in association with neurofibromatosis.

**Pathology**—The neurofibromata consist of reticular connective tissue, with a few nerve fibres—myelinate or amyelinate—winding about either singly or in thin bundles. In places are seen cells "with long hair-like tails," arranged in sheaves or palisades, and proved by stains to be collagenous and fibro-gliai. Hyaline degeneration of the connective tissues precedes jelly-like deposits—the cyst-like lesions—into which haemorrhage may occur (Kinnier Wilson 1940). In plexiform neuromata and elephantiasis there is loose connective tissue containing nerve strands "fantastically overgrown." The skin tumours are practically pure fibromata: only a small proportion include nerve fibres.

As to the bone lesions, the neurogenic origin of those which are subperiosteal is readily acceptable, but this is not so with those which are endosteal. Nevertheless the typical fibrosis with "whorls" of cells has been found in some lesions apparently endosteal. Uhlan and Grossman (1940) found "whorls" both in a soft tissue tumour and in the underlying cystic jaw of a girl of sixteen years. An intra-osseous neurofibroma was found at the site of a spontaneous fracture of the tibia in a girl of seven years (Green and Rudo 1943) and, as already referred to, in a leg amputated for sarcoma (Norley et al. 1945). Neurofibromatous tissue may or may not be found at the site of a pseudarthrosis.

We have discovered no clear statement as to the nature of the pathological changes in a bone showing diffuse increased density with neither cyst formation nor erosion of the cortex by a subperiosteal neurofibroma: Tanner (1946) considers that sclerosis is a late development and follows earlier rarefaction and softening. Collagenous and myxomatous degeneration in osseous lesions, with formation of cysts containing brownish fluid (the result of haemorrhage) are mentioned by Thannhauser (1944).

The cause of the scoliosis where there is no cystic or other lesion in a vertebral body is
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obscure. There is usually no definite evidence of paralysis, but this may occur when a spinal root is the seat of a neurofibroma. Eden (1941) reported a case with multiple "dumb-bell tumours" of the posterior roots. In ordinary cases he likens the scoliosis to that seen in syringomyelia. It has been suggested that the deformity is due to derangement of tonic nervous control of the vertebral muscles.

Diagnosis—This should present little difficulty. The cutaneous nodules and subcutaneous neurofibromata should distinguish neurofibromatosis from polyostotic fibrous dysplasia with areas of pigmentation. These areas are smooth and generally much larger than the café-au-lait spots of neurofibromatosis. The bone changes may be somewhat similar.

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CASE 19—NEUROFIBROMATOSIS

(Figs. 47 to 49.) Female, aged twenty-one years. Complained of shooting pains, from the little toe up the back of the right leg to the hip, for the previous ten weeks. Pain not affected by exercise or rest. Swelling at back of right thigh as long as she could remember: painless until present attack. Pigmented areas of skin present since birth. Family history, negative. On examination—dark-skinned woman. Pigmentation on outer side of right ankle, back of
leg, whole of thigh, and both buttocks extending forwards on to abdomen. On the pigmented area of thigh there were circular black spots. Hairy mole on left buttock. Pigmented spots on chest and arms and pigmented patch on left ankle. Pain confined to pigmented area of right leg. Swelling on back of right thigh felt like a loose bag of skin, partially filled with fat containing hard round masses. Liver slightly enlarged. Diminished sensibility to pinprick in the area corresponding to the pain. Mild scoliosis. Temperature swinging to 100 degrees. Radiographs showed increased density of the shafts of the major long bones of the right leg, especially the femur, in which the density ends below in streaks. A cortical indentation is seen on the inner side of the upper third of the shaft of this femur, possibly the site of a periosteal neurofibroma. The lumbar vertebral bodies are relatively deep, and the transverse processes more slender than usual. (Under the late Dr Douglas Firth.)

Fig. 47

Fig. 48.

Fig. 49.

Case 19. Figure 47—Pelvis and hips, showing the slender pubic and ischial rami, sharp lipping of the lower margin of the right anterior superior iliac spine and of the margins of the great trochanters. Note the narrow joint space of the right hip, the exuberant rounded lipping on the femoral head and also on the lesser trochanter. Figure 48—Right femur and knee joint, showing distortion of the posterior surface of the shaft, and increased density, ending below in streaks. Note indentation of the cortex on the inner side of the upper third of the femoral shaft, and a suggestion of abnormal density in the tibia. Figure 49, Lumbar spine showing the vertebral bodies relatively deep and the transverse processes more slender and spicula

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