RADIOLOGICAL FEATURES OF NEUROFIBROMATOSIS

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Von Recklinghausen [1] in 1882 first established the true nature of the tumours in this disease. Lichtenstein and Jaffe [2] (1942) consider that the underlying cause is a fundamental genetic defect, but according to Willis [3] (1948) the absence of a family history is not unusual.

The primary characteristic of the disease is the development of cutaneous and subcutaneous tumours arising from the peripheral nerves; but there are, however, many other features, which are summarized by Friedman [4] (1944) as (1) pigmentation of the skin, (2) mental deficiency, (3) involvement of the central nervous system, (4) congenital developmental defects, and (5) alterations in the skeleton.

Brooks and Lehman [5] (1924) were apparently the first to draw attention to local bone changes, such as subperiosteal and cortical 'cysts'. A condition of 'neurofibromatous elephantiasis' was found in 2 of the 7 cases they described. According to Weber [6] (1930) this term

is applied to an extreme degree of plexiform neuroma and pachydermatocele of the soft parts of an extremity. He expresses the opinion that more or less diffuse neurofibromatous thickening of the periosteum is likely to be present in these cases to account for the bony hyperplasia. He thinks that the latter is intimately connected with excessive blood supply. The incidence of skeletal changes in neurofibromatosis is quoted as 7% by MacKenzie [7] (1950) and Friedman [4] (1944), though Holt and Wright [8] (1948) reviewing 127 cases over a period of 13 years (1934-1947) find the incidence higher. The bony changes are well summarized by MacKenzie. He points out that the erosive defects are frequently due to pressure, for they bear a close relationship to the soft tissue lesions. He states that the disorders of bone growth include both atrophy and hypertrophy, sometimes concurrently at different sites of the same bone

Moore [9] (1941) expresses the opinion that a growth distortion or faulty control of growth accounts for the occurrence of hypertrophy and under-development. This growth disturbance is also the underlying factor in the pseudarthrosis cases, usually seen in children.

According to Fairbank [10] (1951) the neurogenic origin of the subperiosteal bone lesions is readily acceptable, but this is not so with those that are endosteal. Nevertheless the typical fibrosis with 'whorls' of cells has been found in some lesions apparently endosteal. MacKenzie [7] holds that the intraosseous cystic areas are due to lesions of nerve endings which penetrate into the bone with the nutrient vessels, but does not submit any proof.

Friedman [4] reported one case where biopsy from a femur showed growth in marrow spaces which closely simulated neurofibromatous structure, suggesting that nervous tissue must be present in the bone marrow.

A kyphoscoliosis is a frequent finding in this disease. The deformity is usually most marked in the lower thoracic region. Miller [11] (1936) said it was present in 45% of cases. The cause of the scoliosis is controversial. Gould [12] (1918) thought it was due to bone softening. Brooks and Lehman [5] held that it was caused by neurofibromata of spinal nerves. Moore [9] associated it with growth distortion. MacKenzie [7] thought that it was due either to an associated congenital defect or to asymmetrical erosion of a vertebra.

According to Fairbank [10] the scoliosis usually shows a tendency towards progressive increase of the curves. Paraplegia may develop in cases with severe scoliosis. This may occur when a spinal root is the seat of a neurofibroma.

Spondylolisthesis was first reported in this condition in 1950 by McCarroll.[13] He described 4 cases, and postulated that it was due to congenital pseudarthrosis of the pedicle. He said that the causal relationship to neurofibromatosis was not proven.

McCarroll also quotes cases with marked vascular changes, notably haemangiomata of the diffuse flat type, a plexiform type with dilated veins and lymphatic oedema of hypertrophied extremities.

The occurrence of secondary malignant changes is mentioned by Moore,[9] and MacKenzie [7] states that sarcomatous change may occur in more than one fibroma.

CASE REPORTS

Case 1

A Bantu female aged 29 years, admitted on 14 April 1954 complaining of abdominal pain and swelling of 6 months' duration. Jaundiced for 2 weeks. Numerous lumps all over the body, which started from a single small lump on the left ear—8 years ago.

Examination. Numerous soft, subcutaenous, well-defined, non-tender masses, varying from 2 mm. to 10 cm. over entire body surface. Large swelling of similar nature on lateral side of right thigh. Patient wasted, with marked jaundice and pallor of mucous membranes. In the abdomen: extensive ascites, spleen 5 inches below rib margin, no other masses felt. Remaining systems normal.

Diagnosis: Hypersplenism, haemolytic anaemia and neurofibromatosis.

Special Investigations were made relevant to the hypersplenism and the haemolytic anaemia, but they have no bearing on the neurofibromatosis.

X-Ray. No abnormality discovered in the chest or spine. *Pelvis and Femora:* There were exostoses and some bone proliferation on the lateral aspect of the right ilium, which was flattened. There was a rounded ossification about the size of a hazel nut just above the upper border of the greater trochanter of the right femur. The greater trochanter was flattened on its lateral aspect and showed areas of increased density. It was thought probable that these

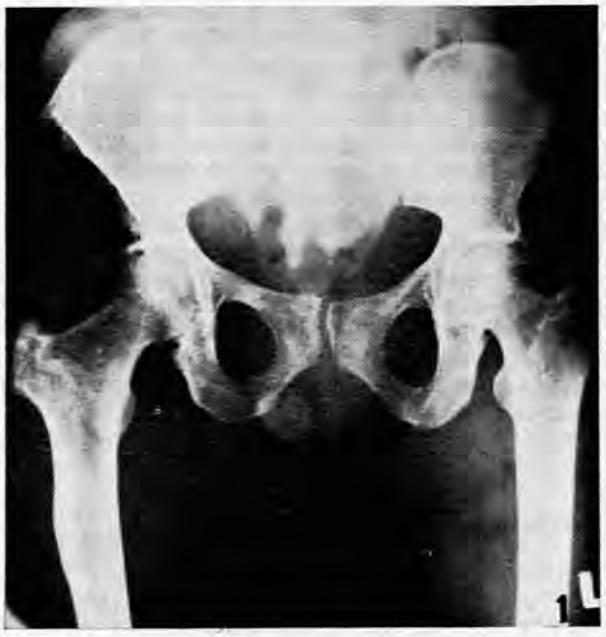


Fig. 1. Case 1. Showing exostoses and bone proliferation of right ilium, with flattening of lateral aspect.

bone changes were related to the soft-tissue mass on the lateral aspect of the upper thigh, which was suspected to be due to neurofibromata. In high intensity light it could be seen that there were multiple small calcifications in the soft-tissue tumour mass on the right side of the thigh. (Calcifications can occur in lipomata but are not usually seen in neurofibromata.) There was an effect of extrinsic pressure on the cortex of the upper end of the femur.

The patient died on 29 April 1954.

Case 2

A Bantu female aged 17 years, admitted on 9 August 1953 complaining of swelling on outer border of left foot. This commenced 2 years ago and was operated on at another hospital and recurred within 2 months. From the time of origin of the swelling

the bony architecture of the foot had gradually collapsed and walking was at times extremely painful. A similar swelling removed from over the left clavicle did not recur, but a keloid developed in the scar. A 3rd swelling developed near the external meatus of the right ear 4 months back and was gradually increasing in size.

Examination. A soft swelling occupied the right external auditory meatus and appeared to be attached to both sides of the external auditory canal. There was also a soft ill-defined swelling over the antero-lateral aspect of the left foot (4 × 3 inches) with an operation scar over the swelling. Crepitus could be elicited at the ankle joint.

Diagnosis: Multiple lipomata, neurofibromata, synovioma.

X-ray. There were cyst-like areas in the bases of the 3rd, 4th and 5th metatarsals and in the tarsal bones. The bones affected showed some alteration in size and outline as compared with the bones of the right foot. Some of the intertarsal joint-spaces were enlarged,

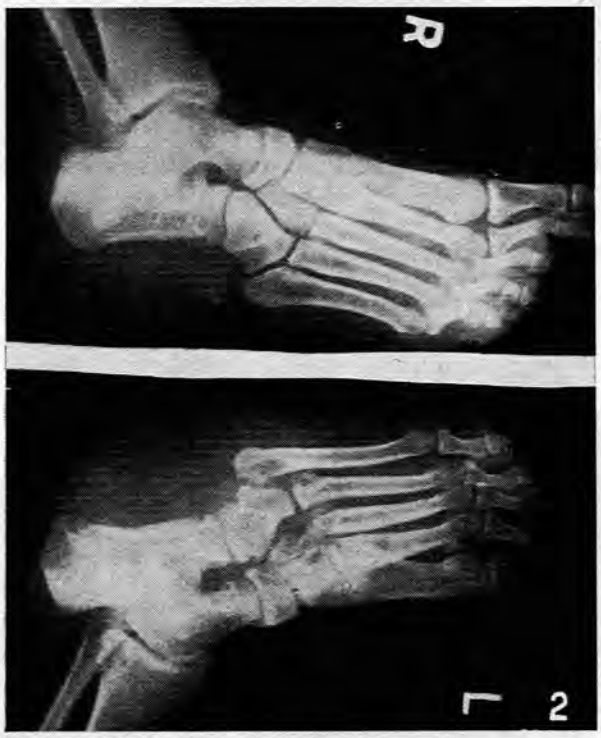


Fig. 2. Case 2. Showing deformity of tarsal bones.

best seen in the oblique views. There was associated soft-tissue swelling on the lateral aspect of the foot, with a marked varus deformity and some pes-cavus deformity. The appearances were considered to be due to neurofibromatosis.

Biopsy of meatal tumour: Plexiform neurofibroma (Dr. E. Roach).

Complete removal of the meatal tumour was found to be impossible.

Case 3

An Indian male aged 7 years, admitted on 27 February 1948 with a diagnosis of acute osteomyelitis of his right foot. This apparently developed after injury 7 days previously.

Examination. Child was in poor condition with a diffuse swelling of the right leg and foot. It was extremely tender, with medial fluctuation. Temperature 99°F. Other systems normal.

Operation. Incision along medial aspect lower leg; much pus drained.

X-Ray reports at this time were consistent with an osteitis, and a review of serial reports suggests that radiographically the response was rather tardy. Penicillin and sulphadiazine were administered. Unfortunately these films have been discarded and are not available for review.

Subsequent healing took place.

Readmission. The case was readmitted on 21 July 1953 for a 'lump' on the back, but this appeared to be due to extreme scoliosis, the curvature being to the right in the thoracic region. On examination the right glutei appeared to be weak; apart from general wasting no other abnormality demonstrated. Diagnosis was made of old poliomyelitis.

X-Ray. The spine showed gross lumbo-dorsal scoliosis, with atrophy and variation of the normal trabecular pattern of the bodies in this region. The lateral view indicated that there was anterior bulging of the posterior vertebral margins of the lower dorsal vertebrae, with resultant widening of the spinal canal and intervertebral foramina. The transverse processes of the bodies in this

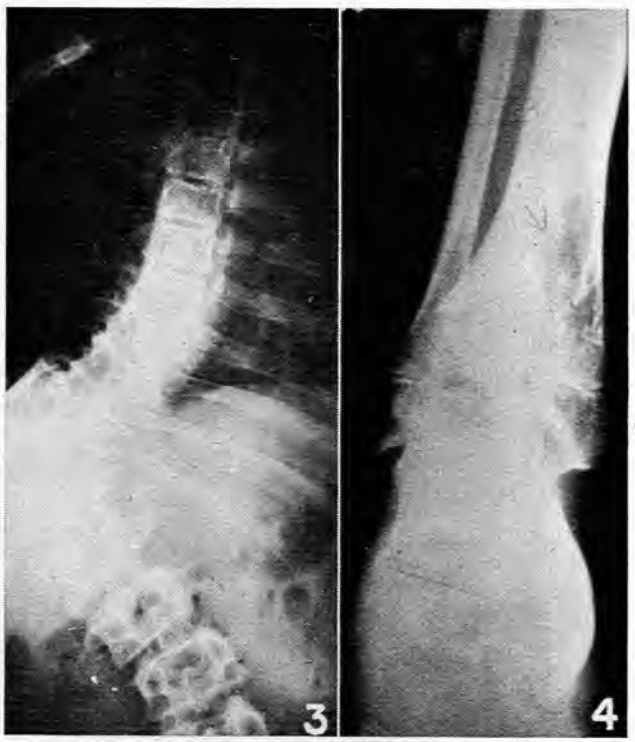


Fig. 3. Case 3. Showing gross lumbo-dorsal scoliosis with atrophy of transverse processes and vertebral extremity of 12th rib.

Fig. 4. Case 3. Showing old osteitis with cystic change.

region appeared to be atrophic and this was well seen in the antero-posterior view. The 12th rib showed atrophic thinning of its vertebral extremity. The appearance was considered to be highly suggestive of neurofibromatosis of the spine. Skeletal survey demonstrated a cystic oval area of the distal and medial aspect of the right tibia showing coarsening of trabeculation. Sclerosis on the lateral aspect had developed, and deformity of growth was that of a valgus deformity. The appearance was thought to represent a neurofibromatous lesion.

The chest film revealed no pulmonary abnormality. The right cardio-phrenic angle was occupied by the convexity of the scoliotic spine.

At the time of this X-ray report it was not known that the patient had been previously admitted for osteitis of the right tibia. When this information became available the tibial lesion was reviewed. It was then thought to represent an old osteitis with cystic change. This particular cystic type of end-result was, however, felt to be unusual, and it was subsequently suggested to us [14] that the lesion was due to infection in a neurofibromatosis deposit following trauma. Re-examination of the patient revealed numerous plexiform subcutaneous neurofibromata associated with *café au lait* skin pigmentation.

Case 4

A Native male aged 18 years, admitted on 20 August 1954 complaining of gross swelling of the right leg from early childhood. The patient stated that he was born with his 4th and 5th toes deformed, and from early childhood his right foot became progressively bigger. It was not painful except for an area over the heel and he said he could walk well enough.

Examination. Gross enlargement of right lower leg, firm and non-tender; does not pit on pressure. There is a fluctuant area over the heel. No increase of skin temperature as compared with other limb. No bruit. Femoral artery palpable. There are distended superficial veins on thigh. There is also a large soft swelling 6 × 3 inches on right buttock, superficial and non-tender. There are similar but smaller swellings all over the trunk. On questioning the patient said these had been present since his leg started swelling. Bilateral gynaecomastia present. Pus was aspirated from one of the leg swellings.

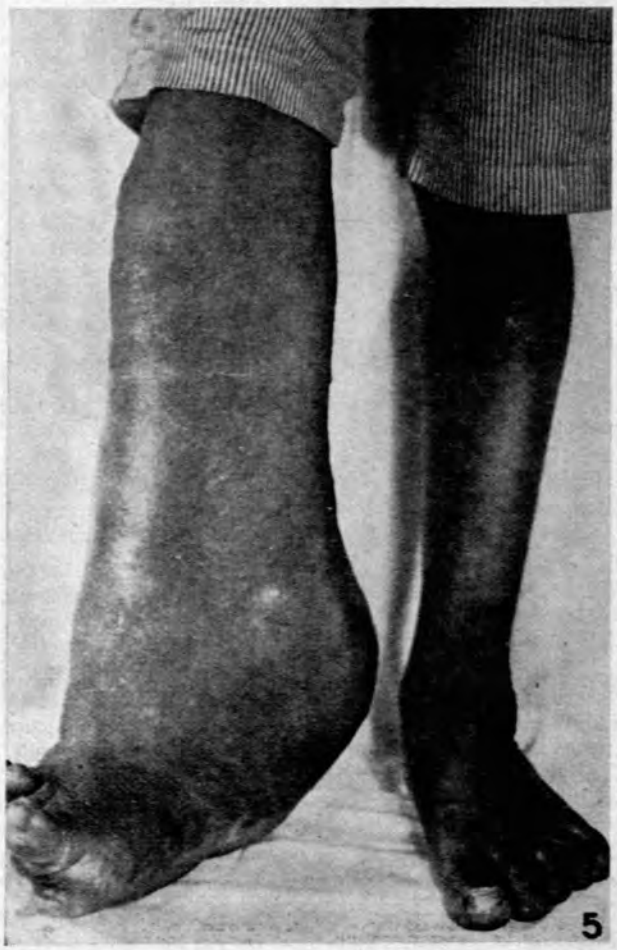


Fig. 5. Case 4. Showing gross swelling of right lower leg.

Nothing abnormal found in the *central nervous system*, the *cardio-vascular system*, or the *chest*.

Diagnosis: Neurofibromatosis, lipomatosis, phlebectasia.

X-Ray. There was a massive soft-tissue swelling in the lower half of the right leg, extending posteriorly and more medially than laterally. The tibia and fibula were widely separated. There was some localized cortical thickening on the posterior aspect of the middle third of the cortex of the tibia. The bones of the right foot were decalcified and showed areas of bone defect, particularly the

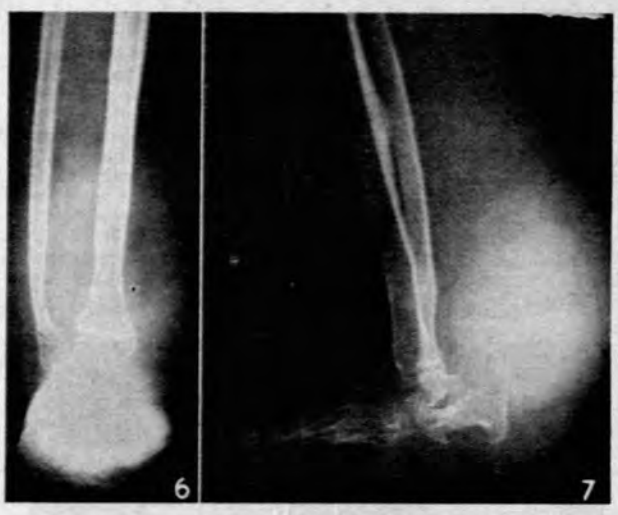
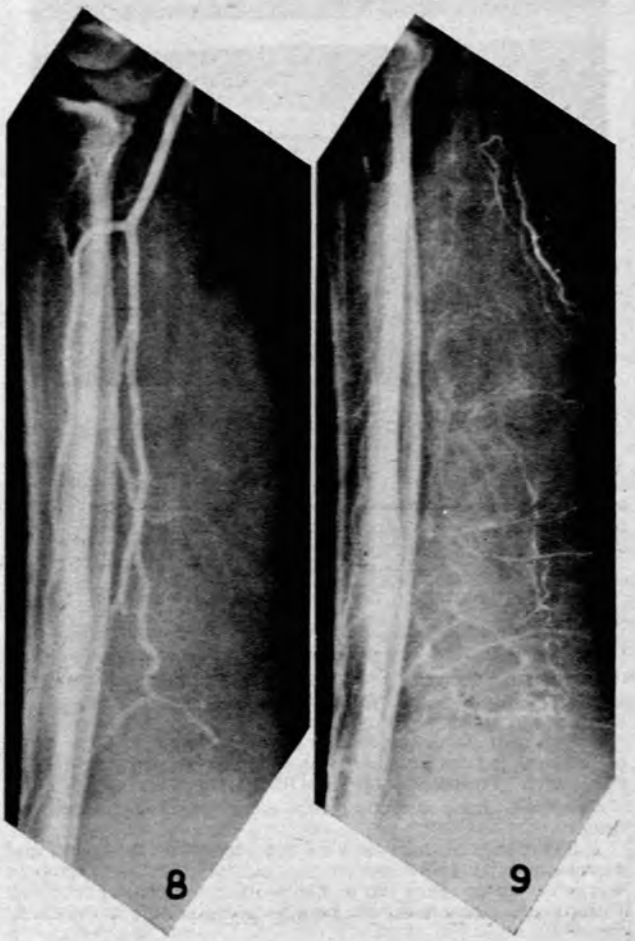


Fig. 6. Case 4. Showing separation of tibia and fibula.

Fig. 7. Case 4. Showing localized cortical thickening on the posterior aspect of tibia and the gross alteration in the bones of the foot.



Figs. 8 *and* 9. Case 4. Arteriograms.

os calcis and the cuboid. In the upper end of the right tibia there was an elongated oval area of bone absorption. A review of the skeleton did not show any other obvious changes except that a small transradiant area was seen in the upper end of the descending ramus of the ischium on the right side. The pelvis was seen to be deformed and the right femur externally rotated. There appeared to be an old healed fracture of the horizontal ramus of the left pubis. There was lumbar scoliosis convexity to the right. No well-defined transradiant areas were seen in the soft-tissue tumour mass in the right buttock.

The radiologist favoured a diagnosis of neurofibromatosis on account of the bone changes in the foot but did not exclude the possibility of lipomatosis. To exclude a vascular tumour he suggested that an arteriogram should be done. The possibility of a Kaposi sarcoma was considered.

A *Right Femoral Arteriogram* (31 August) revealed a reduced rate of flow, splaying of the vessels in the lower third of the calf, and a fine network of abnormal vessels at this level. It was found subsequently that the splaying and abnormal vessels were at the site of a haemorrhagic tumour, with sarcomatous change.

Skin Biopsy (7 September) revealed an ill-defined fibromatosis nodule, with a few hypertrophied nerve bundles as seen in a plexiform neuroma (Dr. J. Wainwright).

Operation by Mr. Stafford Meyer (23 September). Mid-thigh amputation. Evidence of gross neurofibromatosis of superficial nerves was present. The sciatic nerve was grossly thickened (1 inch thick); it was ligatured and cut.

Detailed Appearance and Histology of the Specimen (Dr. J. Wainwright).

Elephantiasis Neurofibromatosa. There is gross enlargement of the amputated limb due to a diffuse plexiform type of neurofibromatosis of the soft tissues. The sciatic nerve is grossly thickened and nodular at the site of amputation and other nerves show similar distortion.

At the ankle there is a large spheroidal haemorrhagic tumour which shows sarcomatous change. A similar smaller sarcomatous nodule is seen below the knee joint. These sarcomatous tumours appear to have grown expansively and show no involvement of bone. The bones, particularly the tarsal bones, show marked atrophy of the trabeculae, probably due to disuse.

There is infiltration of the cortex of the bones by the neurofibromatous tissue resulting in lacunar absorption of the compact bone, and widening of the Haversian canals.

In places there has been deposition of new-woven bone on the eroded bone surface. Fibrils of the tumour tissue appear to be incorporated in this new-woven bone.

The sections clearly indicate infiltration of the bones by the neurofibromatous tissue from without, and show no evidence of primary neurofibromatosis of the bones.

Case 5

A Native male aged 15 years, referred from Port Shepstone Hospital with diagnosis of spondylolisthesis L5, and admitted on 26 April 1950.

Examination. Abdomen distended owing to lumbar lordosis. No abdominal masses. No rigidity. Generally—a diffuse neurofibromatosis.

X-Ray Report (Dr. F. Gillwald, 3 May). (1) There is a gross spondylolisthesis between L5 and S1. (2) The bodies of L3, 4, 5 and S1 show considerable irregularity of density, with posterior depressions and widening of the intervertebral foramina. The

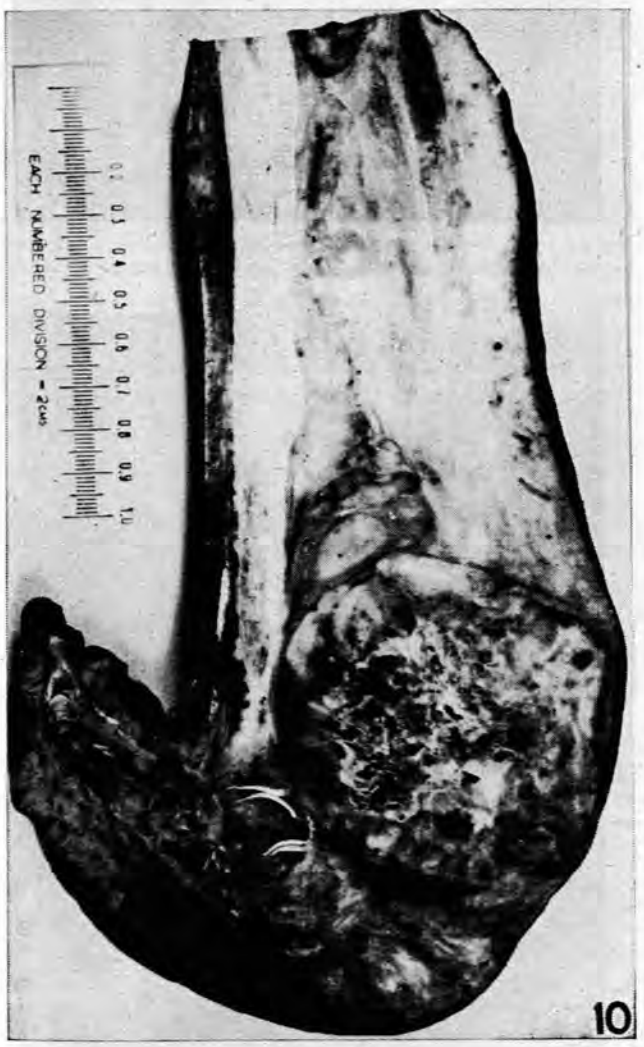


Fig. 10. Case 4. Vertical section of amputated leg showing neurofibromatous tumour and the large area of sarcomatous degeneration. The destruction of the tarsus is demonstrated.

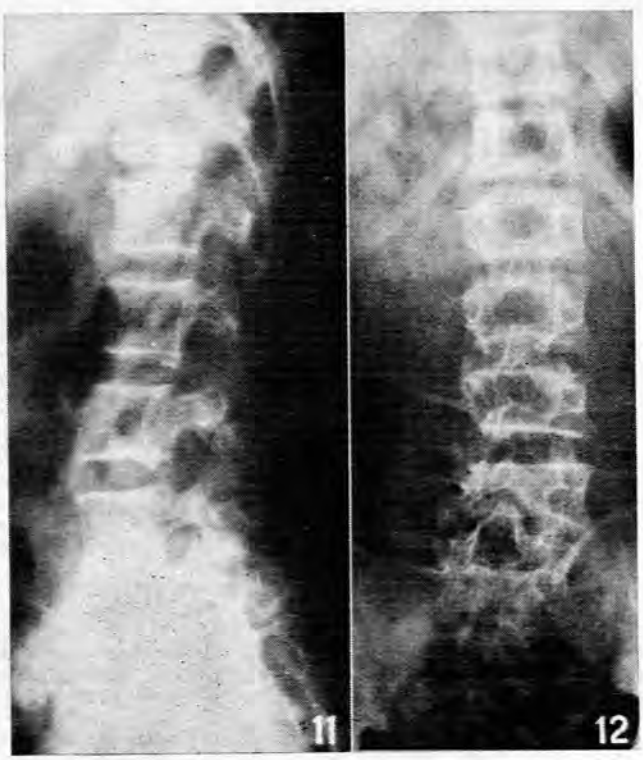


Fig. 11. Case 5. Showing spondylolisthesis between L5 and S1 and posterior depressions of vertebral bodies and widening of intervertebral foramina.

Fig. 12. Case 5. Showing erosion of pedicles on right of L4 and L5.

pedicles on the right of L4 and L5 appear to be eroded and there is a scoliosis and rotation of the vertebrae at this level. The disc spaces are intact. The appearances are those of a neurofibromatosis.

Operation (11 May). Through antero-lateral 6-inch incision, a 3-inch tibial graft taken from right tibia and wound closed. Approach through right lower paramedian incision and pelvic peritoneum opened for 2 inches over the body of S1, just to the right of the mid-line; with small chisel lower surface of L5 traumatized and hole made obliquely into body of S1. Tibial graft down into S1 against inferior surface of L5. Pelvic peritoneum sutured and abdominal wound closed.

Case 6

A Native female aged 57 years, admitted on 7 December 1954 complaining of a large growth arising from the right ankle. The patient stated that this had been there since birth, but had increased in size until it had reached the stage of interfering with her walking. Numerous smaller lumps covered the body.

Examination. The body swellings were soft and were not attached to deeper tissues. The growth surrounding the right ankle appeared to be formed by markedly thickened skin encasing numerous

Fig. 13. Case 6. Antero-posterior view of tumour.

lobulated tumours. It extended down to the ground tending to envelop the foot, and when viewed from the rear, closely resembled the leg and foot of an elephant. General examination of the patient revealed no other abnormality. The diagnosis was that of generalized neurofibromatosis.

X-Ray Report. There is a gigantic soft-tissue tumour of the lower half of the leg, more extensive posteriorly than anteriorly. The tarsal bones are deformed, and the talus and os calcis show areas of bone defect and apparent erosion. The remaining tarsal bones show a distortion of trabecular pattern. The appearances are consistent with the clinical diagnosis of neurofibromatosis.

A review of the skeleton does not reveal any other bone lesions.

A femoral arteriogram reveals that the tumour is extremely vascular, with marked displacement of the vessels, particularly of the posterior tibial artery. There is no appreciable delay in clearing of the dye considering the bulk of the tumour. There are no localized areas of stasis or pooling of dye to suggest malignant change. The venous channels are also dilated.

Operation (Mr. A. Beiles). The patient refused amputation, but agreed to an attempt at removal of the main bulk of the ankle tumour. An incision was made at the lateral aspect of the lower leg, and the posterior tibial vessels were ligated. Skin flaps were made and the tumour was dissected from above. It was extremely difficult to define the anatomy, but as much of the tumour as possible was removed.

Histology. Dr. J. Wainwright diagnosed Elephantiasis Neurofibromatosa. He reported diffuse neurofibromatosis involving collagenous tissues, and no evidence of malignancy.

DISCUSSION

1. In regard to the characteristic deformity of bone and the change in the trabecular pattern, review of the litera-

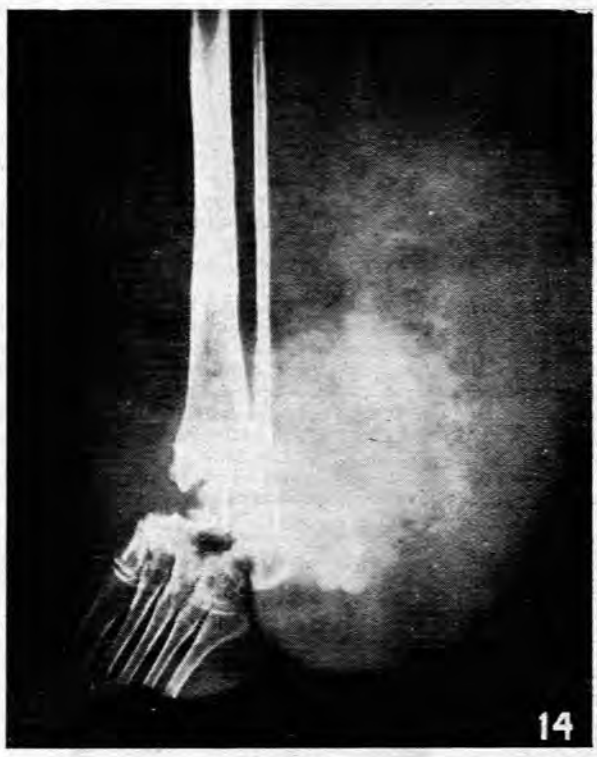


Fig. 14. Case 6. Showing tumour and bone changes in tarsus.

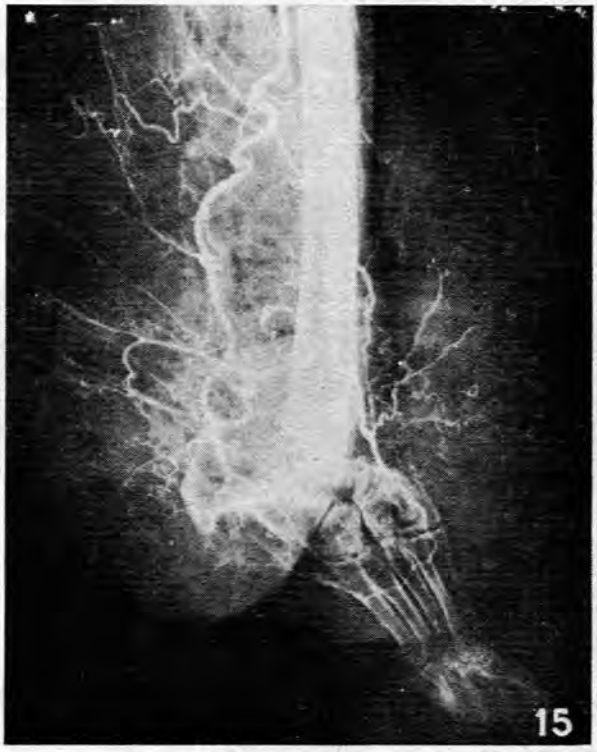


Fig. 15. Case 6. First phase of arteriogram showing increased vascularity and displacement of vessels.

ture and the study of our cases appear to indicate

(*a*) That the deformity is due to a large extent to extrinsic pressure.

(*b*) That there is infiltration of the bones by the neurofibromatous tissue from without. An excellent opportunity of studying the histology presented itself in case 4. This failed to reveal any evidence of a primary neurofibromatosis of the bones. The unusual pattern of vertebral structure in case 3 is in our opinion peculiar to bone associated with neurofibromatous lesions. It is felt that the contributing factors are:

(i) The gross disturbance of normal growth by the adjacent developing neurofibromata.

(ii) Actual invasion of bone.

There does not appear to be a satisfactory explanation of the reactive bone formation seen in the pelvis in case 1. It may be an irritative phenomenon. There is no proof of the etiology of the so-called intra-osseous bone cysts, but it may be that they appear to be intra-osseous because of proliferative bone reaction after invasion from without.

2. Scoliosis apparently occurs as an associated congenital defect, and its frequency has been mentioned in our review of the literature. It appears that it may be present without the curious twisted, almost fragile, deformity of the vertebrae found together with a gross lumbo-dorsal scoliosis in case 3.

3. Spondylolisthesis is apparently a spinal change rarely reported. In case 5 it was the main presenting feature and the reason for referring the patient to our hospital for orthopaedic control of the condition. It was only after radiological investigation that the associated neurofibromatosis was recognized.

4. We have not found any references in the literature to arteriography in this disease. In case 4 (neurofibromatous elephantiasis) are found splaying of the vessels, reduced rate of flow, residual abnormal-looking vessels, at a level which was subsequently found to be the site of sarcomatous change in a haemorrhagic tumour.

5. An impression is gained that the incidence of this disease is relatively high in the Bantu of Natal. Only 1 of the 6 cases reported was an Indian. One of us (M.F.), working for a number of years in Transvaal non-European hospitals, can recall only one case of bone changes in neurofibromatosis.

We are indebted to Dr. S. Disler, Superintendent of King Edward VIII Hospital, for permission to submit this paper, to the surgeons and physicians for their valuable co-operation, to Dr. J. Wainwright for the histology and photographs of specimen in case 4, and to Miss M. McLaggen, Department of Medical Photography, Wentworth Hospital, for the X-ray reproductions and case photographs.

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