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HYPERPARATHYROIDISM WITH RENAL CALCINOSIS

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Clinical knowledge of hyperparathyroidism can be said to date from the successful removal of a parathyroid adenoma in a case of hyperparathyroidism by Mandl in 1926. Since that time Albright and his associates (1929, 1934, 1936, 1937, 1938, 1941, 1948) have played a leading part in advancing our knowledge of the disorder, particularly in regard to the chemistry and to the involvement of the kidneys. It is from the latter angle that we wish to present an interesting case. The problem is not free from complexity, in so far as primary hyperparathyroidism (whether due to a parathyroid adenoma or general parathyroid hyperplasia) may cause renal calcinosis with ultimate renal insufficiency; and, on the other hand, renal insufficiency from any cause, associated with retention of phosphorus and with high plasma inorganic phosphorus, may be followed by hyperplasia of the parathyroid glands, which from a teleological point of view has the purpose of an attempted elimination of the (excessively) retained phosphorus, the primary action of parathyroid hormone being believed to be augmented elimination of phosphorus.

Further, whatever the nature of the primary renal lesion may be, the secondary hyperplasia of parathyroid glands may lead to renal calcinosis and sometimes to osteoporosis. Unless, therefore, the whole history of any one case is known and the case has been investigated in its early as well as its late stage, it may be difficult, or impossible, to state in the terminal phase whether the condition was primary hyperparathyroidism with secondary renal involvement or primary renal disease with secondary parathyroid involvement. Renal calcinosis as a consequence of primary hyperparathyroidism is not only met with clinically but has also been produced experimentally (Hueper, 1927; Leberman, 1940). The calcium may be deposited profusely in minute particles both in the renal parenchyma and in the tubules, and/or renal calculi of variable size may be visible radiologically.

In some urological clinics it is an obligatory routine to test for hyperparathyroidism in every case of renal calculus, and experience has shown that such calculi need not be obviously multiple or bilateral. Perhaps the most complex case of all is the one starting with a parathyroid adenoma with secondary renal calcinosis, in which the

adenoma is successfully removed, but, nevertheless, the renal calcium deposits do not disappear and the damage already done to the kidney is irreversible and even progressive, so that the condition progresses to renal insufficiency, and, secondary to this, there is hyperplasia of the remaining parathyroid glands, the patient ultimately dying in uraemia. Such appears to be the sequence of events in the case here presented.

Case History

A woman of 40 was admitted to a surgical ward of Willesden General Hospital in September, 1941, under Mr. F. W. M. Pratt, with a firm swelling in the middle of the right tibia, said to have followed slight trauma in that area six months previously.

X-ray examination was carried out on September 4 and the radiological report (Dr. Rohan Williams) was as follows: "On the anterior aspect of the shaft of the right tibia, extending over a length of 3 cm., there is a destructive bone lesion associated with minimal swelling of the soft tissues. The bone destruction is confined to the cortex and there is no reactionary new bone formation. The appearances are suggestive of a malignant bone tumour or possibly the rather rare subperiosteal type of osteoclastoma" (Fig. 1).

Mr. Pratt explored the swelling, found a soft-tissue mass under the periosteum, and took out a piece for biopsy. Pathological report: "Typical osteoclastoma." Mr. Pratt then undertook a wedge resection of the tumour. Pathological report: "Wedge of bone with elliptical piece of skin and subcutaneous tissue over one part. To one side beneath the soft tissues is a small deep red 'tumour' extending about 1.5 by 0.5 cm. Microscopy: The histology of the tumour is similar to that of the biopsy—an osteoclastoma. There is some coarse-fibred bone at the periphery of the tissue."

The wound healed and the patient was seen again by Mr. Pratt in September, 1942, with a history of swelling of the left forearm, following trauma. The radiological findings (Dr. Rohan Williams) were as follows: "(1) Left ulna: Two distinct osteolytic cyst-like areas are present in the shaft of the ulna. At each site the cortex is appreciably thinned by the cystic process and there is diffuse decalcification of the forearm bones (Fig. 2). (2) The skull shows a widespread stippled type of osteoporosis affecting the whole calvarium, being especially marked in the fronto-parietal regions (Fig. 3). It should be noted that this lateral radiograph of the skull was taken with 60% of the normal exposure, and, even so, the region of the vault on the film

has been subjected to chemical reduction. (3) Other bones : There are several areas of localized bone destruction—for example, in the left ilium near the sacro-iliac joint, the left lesser trochanter, and the left pubic bone. (4) There is considerable generalized osteoporosis of the skeleton with marked cortical thinning."

The findings appeared to be typical of generalized osteitis fibrosa cystica (hyperparathyroidism), and Mr. Pratt asked

FIG. 1.—Radiograph taken on September 4, 1941, showing the bone lesion in the right tibia.

one of us (S. L. S.) to investigate and advise from this standpoint. The more recent past history, apart from the bone incidents, included constipation, weakness, dyspnoea, and insomnia. The patient was thin and had a small swelling in the lower region of the left lobe of the thyroid gland. There were no signs of thyrotoxicosis. B.P. 120/80. Fundi normal. Urine normal. Serum calcium, 15.8 mg. per 100 ml.; plasma inorganic phosphorus, 2.5 mg. per 100 ml.; plasma alkaline phosphatase, 65 K-A units per 100 ml. Urinary calcium over a three-day period on a daily intake of 100 mg. of calcium was 1,232 mg. Radiographs of the renal tract showed a single small calculus in the lower pole of the left kidney and several small stones in the right kidney (upper half).

The diagnosis of hyperparathyroidism explained all the features, and it was decided to explore the under surface of the left lobe of the thyroid gland for a parathyroid tumour, although the latter rarely presents as a palpable swelling. However, a yellow lobulated parathyroid tumour was found by Mr. Pratt at that site, and removed (October, 1942). Pathological report: "Nodular tumour 2.5 by 1.2 by 1.8 cm. Weight after fixation, 4.4 g. Cut surface: fibrous capsule and deep buff-coloured rather friable soft contents. Some of the material had fallen out, leaving a slightly cystic appearance. Microscopy: a rather uniform tissue resembling normal parathyroid, composed of close-set cells, mainly transitional and water-clear in type. The cells are arranged in masses of varying size, with fine connective tissue septa" (R. R. W.).

Immediate post-operative biochemistry: serum calcium 8.9 mg., plasma inorganic phosphorus 5 mg., alkaline phosphatase 65 units per 100 ml. Six months later: serum calcium 10 mg., plasma inorganic phosphorus 2 mg., alkaline phosphatase 6.7 K-A units

per 100 ml. For some weeks after operation the patient had mild tetany, relieved by calcium and calciferol. Less definite paraesthesias persisted in the next few years, and calciferol, 300 units daily, was given intermittently. One year after operation the radiological bone changes tended to revert to normal: "There is an almost spectacular regeneration of bones within the open areas. Appearance of the upper ulna suggests healing of pathological cystic fracture." Serum calcium 9.9 mg., plasma inorganic phosphorus 2 mg., and alkaline phosphatase 6.7 K-A units per 100 ml.

The patient attended at infrequent intervals at the out-patient department, but the notes do not indicate any serious complaints or findings in 1943 or 1944, and the blood pressure was normal 120/80. In January, 1945, the serum calcium was 11.8 mg. and plasma inorganic phosphorus 3.7 mg. per 100 ml. In October the patient complained of headaches. The blood pressure was 150/90. The serum calcium was 9.8 mg., plasma inorganic phosphorus 6.6 mg.,

and alkaline phosphatase 7 K-A units per 100 ml. The raised plasma phosphorus indicated renal impairment. At this time radiological examination showed partial bony obliteration of the cystic changes in the left ulna. In general, the long bones showed normal architecture, but there was mottled osteoporosis of the skull, vertebrae, iliac bones, and the ribs. The osteoporosis was somewhat unexpected in view of the normal alkaline phosphatase.

FIG. 3.—Radiograph taken on September 14, 1942. A widespread stippled type of osteoporosis is shown, affecting the whole calvarium, especially the fronto-parietal regions.

The patient was not seen again until June, 1946, when she was admitted to hospital after falling off a bus and bruising her right arm. Apart from this, her complaints were dimness of vision and swelling of the ankles in the past few weeks. At this time, however, the florid picture of azotaemic nephritis with cardiovascular hypertrophy was obvious: B.P. 240/160; bilateral papilloedema with albuminuric retinitis and exudates in the fundi; albuminuria with granular, hyaline, and epithelial casts; blood urea 86 mg., 94 mg.; urea clearance only 18% of normal; and severe secondary anaemia. The serum calcium was 12.8 mg. and plasma inorganic phosphorus 8 mg. per 100 ml., the latter high value being due to poor renal function. Radiological examination again showed marked generalized decalcification of all the bones. The plasma phosphatase was reported as only 5 K-A units and again 7 K-A units. Calcium urinary excretion over a 72-hour period, with a daily intake of 100 mg., was 854 mg. Radiography showed metastatic calcification scattered in both kidneys. It was concluded that the original renal calcinosis had led to destruction of renal parenchyma and to renal insufficiency, which, in its turn, had led to secondary hyperplasia of the remaining parathyroid glands.

FIG. 2.—Radiographs taken on September 14, 1942, showing diffuse decalcification of the forearm bones.

As there were no obvious remedial measures available the patient was allowed to go home, as she requested, and was admitted a few months later (October, 1946) with incessant vomiting, soon terminating in uraemic coma; blood urea, 224 mg. per 100 ml. (A specimen of blood taken ten minutes after death showed serum calcium 18.4 mg. and urea 520 mg. per 100 ml.)

Necropsy Findings

A rather thin woman with pale skin and grey-brown hair. Cyanosis of lips. Post-mortem staining of lower abdominal wall.

Cardiovascular.—The heart (397 g.) showed some hypertrophy of the left ventricle. The aorta and the coronary and cerebral arteries were only slightly atheromatous.

Respiratory.—Moderate congestion and oedema of lungs.

Alimentary.—The liver was small (1,060 g.) but appeared normal. The pancreas showed post-mortem autolysis. This system was otherwise normal.

Haemopoietic and Endocrine.—The spleen was small (85 g.) but of normal appearance. Lymph nodes—no abnormality noted. The *thymus* measured 10.5 by 2.3 by 0.5 cm. (No sections of thymus were taken.) The *thyroid* was normal in size and appearance, as were the *adrenals*. Two *parathyroids* were found, both on the right at the lower pole of the thyroid. The anterior and larger measured 3.5 by 1.2 by 1.5 cm.; it was coarsely lobulated, partly pale and partly dark red. The cut surface was a pale creamy colour mottled with dark red. The smaller posterior parathyroid measured 2 by 1 by 0.8 cm. and resembled the other. The *pituitary* was enlarged by a roundish lobulated pale tumour 2.2 by 2 by 2.5 cm., the larger part of which was above and outside the sella turcica. The optic chiasma was stretched over the posterior part of the tumour, which had a pale homogeneous cut surface.

Urinary.—The kidneys were markedly contracted, the right weighing 70 g. and the left 60 g. The subcapsular surfaces were granular, the granules being pale. On section the cortex was grossly reduced, the maximum thickness being 5 mm.; the pattern was indistinct, with a stippling of deposits of calcium; tiny calculi were found in some small cortical cysts. The medulla was also stippled with calcium deposits. The cortico-medullary boundary was blurred. The bladder contained alkaline urine with a deposit of triple phosphates and amorphous urates.

Genital.—The uterus, ovaries, tubes, and external genitalia were normal. The mammary glands exuded a milky fluid when cut; this fluid contained 24 mg. of calcium per 100 ml.

Nervous.—There was a cerebellar pressure cone, and the anterior perforated substance was indented by the pituitary tumour.

Osseous.—The calvarium was up to 1 cm. thick; there was some loss of demarcation of outer and inner tables, with obliteration of diploë. The *right humerus* was externally normal, but on the cut surface of the lower part of the head and surgical neck there was an irregular area of 2.5 cm. in diameter, which was solid, and white in colour with red patches. The upper end of the shaft of the *left ulna* was expanded to a diameter of almost 3 cm. over a length of 3.5 cm.; the upper third of the shaft was slightly bowed and slightly angulated on the distal two-thirds. The expanded part had a cut surface of deep red with greyish markings; the cortex in this region was reduced to 2 mm. thick in places. The upper part of the shaft of the *right tibia* showed slight thickening of the cortex and an increase in medullary trabeculation.

These bones were radiographed after removal. The ulna showed "major cystic changes with expansion in upper third of diaphysis with medial bowing, maximal at level of cyst." In the tibia "the merest traces remain of an old destructive process: some medullary calcification of a non-osseous type is present." In the humerus there were "irregular

intramedullary calcific deposits in the surgical neck with some ill-defined cancellous bone destruction—no demarcated cyst wall" (Dr. E. Rohan Williams).

Microscopy

Parathyroids (Fig. 4).—The enlarged glands are composed almost entirely of transitional and water-clear cells, arranged in solid masses closely set together, so that the tissue is decidedly compact. There are very few oxyphil cells.

Bones (Fig. 5).—The cortical bone is much more open in structure than normally, owing to marked osteoclasts. Haversian canals in the ordinary sense are not seen. In their place are much larger and more irregular spaces, filled by fibrous tissue of varying cellularity. The bony tissue itself is correspondingly irregular in disposition and reduced in amount, besides showing changes indicative of rapid resorption and reformation. There are many cement lines, often irregularly arranged and often ending at surfaces; the bone is mostly woven or coarse-fibred. Osteoclasts are numerous, osteoblasts less conspicuous. The bone marrow is widely replaced by an abnormal bony tissue with intermingled fibrous tissue. The reddish mass expanding the upper end of the left ulna is composed mostly of fibrous tissue, of widely varying cellularity, with scanty spicules of bone embedded in it, some of which are being formed, some being eroded.

Kidneys (Fig. 6).—Fifty per cent. of all *glomeruli* are converted into scarred structures, more or less completely hyaline; they lie in hyaline rings, originally Bowman's capsules, and are typical of the ischaemic or arteriosclerotic kidney. Some of them show slight or moderate granular calcification. Nearly 40% of all *glomeruli* show partial hyalinization of their tufts; but none

FIG. 4.—A representative field from one of the enlarged parathyroids found at necropsy. (H. and E. $\times 105$.)

FIG. 5.—A section of skull showing many osteoclasts eroding woven and lamellar bone, with fibrosis of marrow. (H. and E. $\times 56$.)

FIG. 6.—Kidney. Calcification of arterial walls and of tubular basement membrane. (H. and E. $\times 190$.)

of these aforementioned glomeruli, comprising 90% of the total, show any of the changes associated with glomerulotubular nephritis. The remaining glomeruli show, often in addition to the lesions of the second group described above, focal necroses, adhesions, and capsular endothelial swelling. Some of these glomeruli have afferent arterioles showing fibrinoid necrosis. These lesions are of the kind seen in malignant hypertension. The tubules show alternating islands of atrophy and hypertrophy. In the atrophic parts the remaining tubules are embedded in fibrous tissue which is generally poor in cells. The tubular basement membrane is sometimes calcified. Many arteries of varying size show slight, moderate, or marked calcification of intima and/or media. The arcuate and interlobular arteries show intimal and medial thickening of varying degree; in some cases the lumen is totally obliterated. A few of the smaller arteries show fibrinoid necrosis. Calcification of connective tissue in the cortex affects mainly the fine fibres surrounding tubules, both normal and atrophic; in the medulla it occurs in scattered foci. There is patchy lymphocytic infiltration in both cortex and medulla.

Pituitary.—The enlargement is due to a chromophobe adenoma. The remains of the gland are compressed into a crescent about 2.5 mm. thick, in which the normal pituitary cell types are readily recognized.

Other Organs.—Metastatic calcification is found in the vessels of the ovary, uterus, spleen, and myocardium, and in the connective tissue and muscle fibres of the heart. In the vessels of the organs mentioned calcification affects the media, the internal elastic lamina, and the intima, but not necessarily all of these in any one instance. No relationship can be discerned between the distribution of calcification in the vessels of the heart and its distribution in the muscle fibres. Calcification affects the whole cross-section of the muscle fibres, but not the whole length.

The lungs show confluent bronchopneumonia.

Comment on Pathological Findings

Three matters require discussion: (1) the nature of the enlargements of the parathyroids; (2) the renal changes; and (3) the concomitant enlargement of more than one endocrine organ.

(1) The original parathyroid mass that was surgically removed is regarded as an adenoma because it was encapsulated, because no other enlarged parathyroid was found at that time, and because its histology was clearly that of neoplasia and not primary hyperplasia (Castleman and Mallory, 1935). Correspondingly the enlarged parathyroids found at necropsy are regarded as showing secondary hyperplasia, because they were multiple and their histology fits the descriptions given by Castleman and Mallory (1937), Gilmour (1947), and Fritz and Brines (1951), in studies of parathyroid changes following renal disease.

(2) The renal changes in this case are very similar to those described by Anderson (1939) in his study of the renal lesion in hyperparathyroidism, and to those of Case 3 of Morgan and MacLagan (1954) in which bony and renal changes were caused by a parathyroid adenoma. Both papers drew attention to the absence of changes indicative of Bright's disease. In Anderson's paper there is a photograph of calcified tubular basement membrane closely resembling our Fig. 6. As to the terminal uraemia in our case, there can be no doubt that the degree of renal damage was adequate to account for almost complete loss of renal function.

(3) This case presented a parathyroid adenoma, a pituitary adenoma, and an enlarged thymus. Such a state of affairs is rare, but a few other such cases have been reported, and it may be that this kind of condition will be more frequently observed in future now that it has been noted, as has happened in other matters.

Underdahl, Woolner, and Black (1953) described 14 cases from the literature in which a pituitary tumour was associated with hyperplasia and/or neoplasia of the parathyroids, clinical hyperparathyroidism being present in four of the cases and the remainder apparently lacking clinical data.

The majority of the patients were acromegalics, but two, without acromegaly, had pituitary chromophobe adenomas. Parathyroid adenomas were both single and multiple. In four acromegalics there were also present multiple adenomatous islets of Langerhans, in association with general hyperplasia and hypertrophy of the islets. Hypoglycaemia was a feature in two such cases. Underdahl and his colleagues further described eight cases from the Mayo Clinic in which "multiple adenomas and adenomatosis of the parathyroids and pancreatic islets" were the usual findings, together with chemical and often clinical hyperparathyroidism and hypoglycaemia. In four of these cases there was no evidence of a pituitary tumour; in two the diagnosis was acromegaly, and in two chromophobe adenoma; one of the latter showed no pituitary clinical manifestations, and the other, a male, showed hypogonadism. The coexistence of neoplasia with hyperplasia in the pancreas and parathyroids is possibly in keeping with the theory (Simpson, 1951) that neoplasia of endocrine glands may follow hyperplasia. The chromophobe character of the pituitary cells, in some cases, may be secondary to an initial chromophil state. The question whether the pituitary lesion was primary or merely associated remains unanswered.

Black and Ackerman (1950), reviewing 23 cases of parathyroid tumour, reported one case which had also pancreatic and adrenal tumours, and another with tumours also of the pituitary, thyroid, adrenals, and pancreas.

In our case there was apparently enough residual pituitary for normal function, because the adrenal cortex was not atrophic, nor was the thyroid, and there were maturing follicles in the ovaries.

We have found the thymus involved in only one report, that of Bergstrand (1922). In each of his two cases the thymus was regarded as hyperplastic, and in each case both the inferior parathyroids contained small adenomata. No skeletal abnormalities were noted. Unfortunately no sections were prepared from the thymus in our case. Regarding the apparently functionless state of the parathyroid adenomata in Bergstrand's cases, it is worth noting that Hadfield and Rogers (1932) also reported two cases of parathyroid tumour without osteitis fibrosa, one being an acromegalic; and four of the surgical cases of Underdahl *et al.* (1953) mentioned above had no discernible skeletal involvement, though they showed positive chemical findings.

Discussion

As has been indicated above, Albright and co-workers were the first to indicate the importance of renal involvement in hyperparathyroidism, a finding which might well have been anticipated from the experimental work of Hueper (1927), who demonstrated metastatic calcification in organs such as the kidneys, lungs, and stomach, in dogs dying of acute parathyroid poisoning. Cope (1942) reported renal calculi in no fewer than 47 of 67 proved cases of hyperparathyroidism.

Johnson (1939) described a case with the title "primary hyperparathyroidism with extensive renal calcification and secondary hyperplasia of the parathyroids." The patient was a man of 34 who had suffered for two years from weakness, loss of weight, thirst, and polyuria. He entered hospital following a fracture of a cystic right humerus after very slight trauma. Serum calcium was 15.7 mg., plasma inorganic phosphorus 2.6 mg., and plasma phosphatase 34 Bodansky units per 100 ml. Blood urea was normal, but some areas of calcification were noted in what was described as a horseshoe kidney. A parathyroid adenoma was removed, and after a period of mild tetany the blood chemistry returned to normal and the patient was not seen for a period of four years. He then returned with hypertension and uraemia and renal insufficiency, dying in uraemic coma. The renal insufficiency distorted the blood chemistry, so that the serum calcium was only 10.5 mg. and the plasma inorganic phosphorus was above normal—namely, 6 mg. Necropsy showed gross hyperplasia of the remaining three parathyroid glands which could only be regarded as

secondary to the renal insufficiency, nephrocalcinosis, with hyalinization of the glomeruli and deposition of calcium in the tubules and interstitial cells.

Downs and Scott (1941) reported a similar case with the title "hyperparathyroidism with adenoma causing renal failure and secondary hyperparathyroidism." This patient, however, presented in the late stages as a case of renal colic and severe renal insufficiency with terminal uraemia; and the necropsy finding of one parathyroid adenoma and hyperplasia of the remaining parathyroid glands led to the diagnosis and reconstruction of the disease as indicated by the title. The renal insufficiency, in this case also, distorted the calcium and phosphorus values, which were respectively 5.8 mg. and 7.6 mg.—another difficulty in making the diagnosis when renal insufficiency had led to severe phosphorus retention and secondary depression of an initially raised serum calcium.

In our case, although renal calcinosis was present initially, there was every indication that renal function was at that time normal. The blood pressure and the blood urea were normal and there was no cardiovascular hypertrophy. Further, the removal of the parathyroid adenoma led to post-operative parathyroid insufficiency and mild tetany, which would have been unlikely if the remaining parathyroid glands were hyperplastic at the time of the operation. However, although we lost touch with the patient there was no evidence that the calcium deposits in both kidneys ever disappeared, and the changes that they had already produced in the renal parenchyma were probably of sufficient severity to lead to a progressive involvement of the kidneys and finally to renal insufficiency. At a certain point along this road, the remaining parathyroid glands underwent hyperplasia in an attempt to eliminate the retained phosphorus. The high serum calcium value and the low plasma inorganic phosphorus value at the time when the patient was first seen also indicated that the kidneys were then not seriously impaired. In the terminal phase, although parathyroid hyperplasia and hyperfunction were undoubtedly present, the serum calcium was normal, the depression of the raised serum calcium being secondary to the high plasma inorganic phosphorus.

Hellström (1950), in a review of this subject, states: "The prognosis following parathyroidectomy in hyperparathyroidism is chiefly dependent upon the degree of renal damage at the time of operation; the skeletal changes are of less importance. A certain improvement of the renal damage is possible after parathyroidectomy, but in most cases the damage is lasting or shows progression." He further states that "evaluation of the prognosis calls for a long follow-up period, since the patients may be apparently healthy for many years but ultimately die from sequelae of hyperparathyroidism, even if the latter has been checked by parathyroidectomy. The renal damage is an early symptom of hyperparathyroidism and is mainly due to calcium deposition in the tubular epithelium and to vascular changes leading to nephrosclerosis."

From our own case and from the study of the literature we would associate ourselves with the opinion here stated, which was based on a series of 21 cases.

Summary

A case of hyperparathyroidism is described in a woman of 40, presenting itself initially as an osteoclastoma of the tibia. There was also radiological evidence of renal calcinosis secondary to the primary hyperparathyroidism. Removal of a causative single parathyroid adenoma was followed by transient tetany and subsequent return of the blood chemistry to normal. Four years later, however, the patient returned with severe renal insufficiency and terminal uraemia. Necropsy showed nephro-sclerosis with multiple calcium deposits; and hyperplasia of the remaining parathyroid glands, secondary to the renal insufficiency.

Primary and secondary hyperparathyroidism therefore occurred in the one patient at different phases of the disease. In view of the bad ultimate prognosis of primary hyperparathyroidism with secondary renal involvement, through multiple calcium deposits, the importance of diagnosing primary hyperparathyroidism early, and before such renal involvement, is indicated.

The associated finding of a pituitary chromophobe adenoma is also recorded and discussed.

It is with great pleasure that we express our acknowledgments and thanks to Mr. F. W. M. Pratt, who carried out all the surgery, and under whose initial care the patient came; to Dr. E. Rohan Williams for the radiological reports and illustrations, to Dr. G. E. Harre, who carried out the necropsy and initial biopsy studies, and to Dr. G. M. Smith for chemical pathology.

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DIABETIC AMYOTROPHY*

BY

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Although neurological complications of diabetes have been recognized for almost a hundred years, they have not received the detailed attention usually given to neurological disorders, nor the attention they deserve. That they are common is beyond doubt. Joslin *et al.* (1952) saw 913 diabetics with neurological syndromes in one hospital during a five-year period; this list included a number of disorders of the nervous system which were probably coincidental, but 519 consisted of syndromes of areflexia, paraesthesiae, pain, weakness, and wasting, most of which were almost certainly by-products of diabetes. More recently Matthews (1955) has found evidence of "neuropathy" in 37% of 545 unselected diabetics. Since the total number of diabetics in the world is said to be about twenty million it would seem that "diabetic neuropathy" may include millions of victims. The term "neuropathy" is used rather loosely, sometimes referring to disturbances of peripheral nerves only (in the previous sense of "neuritis") and sometimes more widely to include motor and sensory disorders resulting from lesions of the spinal cord,

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