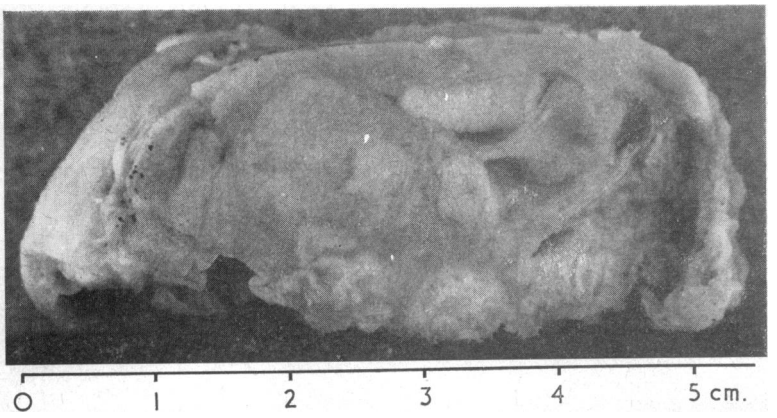

FIG. 1.—Gross appearance of a typical tumour.

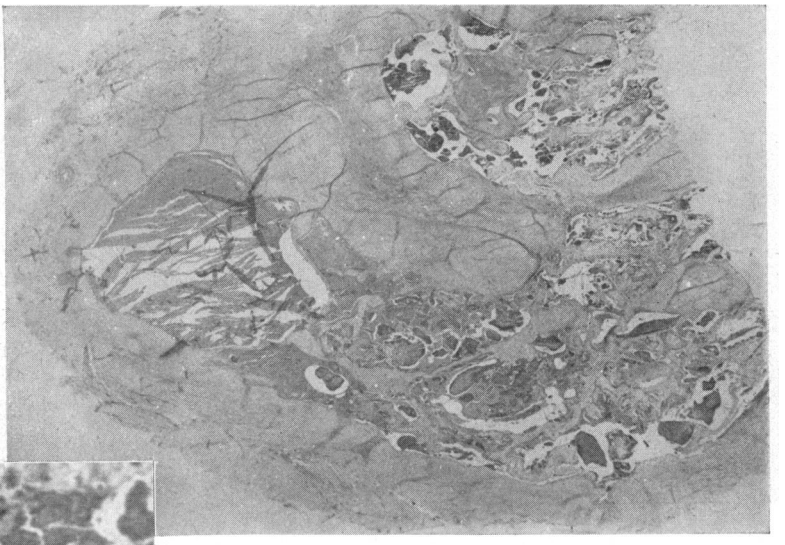

FIG. 2.—Low-power photomicrograph showing a cross-section of a typical lesion with several cysts of varying size containing basophilic material and collagenous plaques.

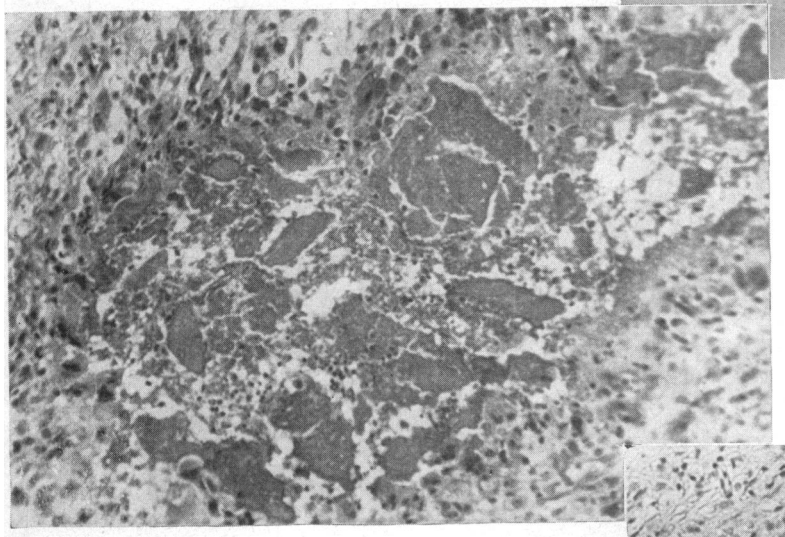

FIG. 3.—Older lesion with degenerating collagen and much fibrous tissue.

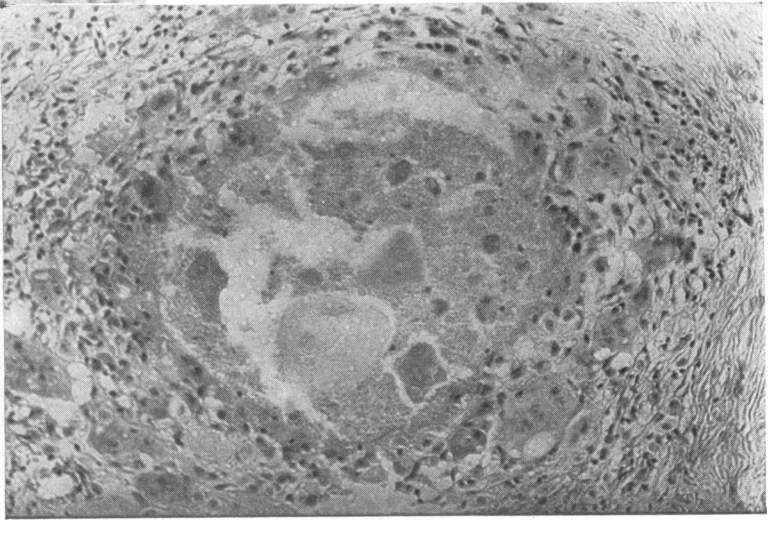

FIG. 4.—Active cyst containing granular material with several collagenous plaques present and surrounded by several layers of multinucleated giant cells.

Tumoral Calcinosis—an Unrecognized Disease

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[WITH SPECIAL PLATE FACING PAGE 143]

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Summary: Twenty-six cases of tumoral calcinosis are reported from Kenya. The disease, frequently misdiagnosed, is of unknown origin. It presents as calcified tumours, usually around the hips and buttocks, in muscle and subcutaneous tissue. The tumours are partly solid, partly multiloculated cysts which contain a chalky fluid. They may grow rapidly or very slowly, and are found in children and adults. Both sexes are affected and there is no obvious tribal or geographical localization.

Introduction

Once in a while one comes across a disease which is so obvious in its clinical manifestations that it should easily be recognized and yet which is frequently misdiagnosed and dismissed as something else. Such a disease is tumoral calcinosis. In countries such as Kenya, where until recent years difficulties in transportation and communication, added to lack of qualified staff, have made histological examination of specimens difficult, tumours have often been consigned to the waste basket and the surgeon has recorded his diagnosis as final. Consequently it is not at all surprising that cases of tumoral calcinosis have masqueraded under such pseudonyms as "calcified bursa," "calcification of a lipoma," "metastatic calcification," and so on. Where nodules such as those of onchocerciasis are common and where a special way of load-carrying by women produces adventitious bursae on the lower back, such as the now vanishing Kikuyu bursa, the situation is even more confused. In fact it was not until one of us (S. M.) discovered that the vector of onchocerciasis, *Simulium naevi*, had been eradicated some years previously from an area of Kenya and that therefore a calcified tumour in a young woman could not be an old onchocercal nodule, since she had been born too recently, that he began to investigate these tumours seriously. The result is that tumoral calcinosis was finally recognized as such.

The purpose of this paper is to present 20 certain and six probable cases of this interesting disease and to report its presence in both Kenya and Uganda.

Until publication of the papers by Palmer (1966) and Thomson (1966) only 25 cases had been reported in the literature. They recorded an additional 50 cases, mostly from Rhodesia, and mentioned seeing others in Nigeria and elsewhere. Professor Michael Hutt, of Kampala, who has studied some of our slides, informs us that three or four identical lesions are seen in Uganda each year. Thus it appears that the disease, while uncommon, is widespread.

A few representative reports follow. Most of these patients were treated in outlying areas or discharged from hospital as soon as possible postoperatively owing to serious shortage of beds. The diagnosis had not been made and so no intensive biochemical or other investigations were done.

Case Reports

Case 1.—An 11-year-old Kikuyu girl from Kerugoya had had a swelling behind the right elbow for three years. The swelling varied in size and movement of the joint was painful. On examination there was a painless, apparently cystic, swelling which stood out prominently when the elbow was fully extended. At operation a well-encapsulated mass attached to muscles and tendons was dissected out. It was incised and exuded a milky substance. The clinical differential diagnosis included chronic bursitis, tuberculous lymph node, and gouty bursitis. The condition was described by the pathologist, but was recognized as a typical tumoral calcinosis only when reviewed by us two years later.

Case 2.—A Kipsigis woman had had a swelling over the left greater trochanter for three months. This broke down with a discharge of offensive pus. *X*-ray examination showed no involvement of the femur. The tumour was incised and a large calcified mass found, with diffuse fibrosis in which calcific areas were noted. A specimen sent to our laboratory was diagnosed as consistent with old calcified onchocerciasis. On review by us it was found to be tumoral calcinosis.

Case 3.—A 12-year-old Luhya boy originally came to Kakamega with a three-months history of multiple soft swellings of both thighs and the left jaw. A biopsy specimen from a site unstated was diagnosed by one of us (S. M.), then new to Africa, as a foreign-body reaction with cyst formation perhaps due to a parasite. Four months later the child was admitted to hospital in Kisumu with a four-months history of three swellings on the right elbow and both buttocks. On clinical examination these appeared to be partly cystic and partly solid. At operation on the left buttock a mass deep to the triceps and gluteus maximus muscle was removed. It was not related to the hip joint. The mass at the elbow was also removed and was noted as being close to the joint capsule. The same pathologist, not knowing this was the same child, made a diagnosis of loculated cysts without parasites and queried the possibility of onchocerciasis.

Case 4.—A Luhya man from Tiriki complained of a swelling present for many years over the left greater trochanter which had recently been growing in size. It was about 5 cm. in diameter and 3 cm. thick, movable, and hard. At operation the tissues were full of small pieces of calcium, and complete excision was impossible. The pathological diagnosis was onchocerciasis with no worms found.

Case 5.—A young Meru man had rapidly growing recent swellings of the buttocks, hips, and right elbow (Fig. I). The *x*-ray films showed massive calcification of the pelvic region (Fig. II) and a smaller nodular calcification at the elbow. No biochemical abnormalities were noted, but as the case records have been lost exact figures cannot now be obtained. A sterile specimen was obtained and cultured for bacteria and fungi. There was no growth.

None of these patients has reported for follow-up and more extensive data are unobtainable: this is one of the so far insuperable problems of working in "developing countries."

Clinical Findings and Pathology

Tumoral calcinosis presents clinically as a swelling, usually painless, in the vicinity of joints. Commonly this is solitary and grows slowly over a period of years, but in a few of our cases there have been multiple and rapidly growing masses up to 7 cm. diameter in three to four months (Fig. I). The mass may be subcutaneous or intramuscular, depending on the location. It is usually firm or hard in consistency but sometimes feels cystic, at least in part. Usually the overlying skin is unbroken, but in a few cases ulceration has been reported. Occasionally there is sinus formation with a white discharge.

The *x*-ray appearances are characteristic (Fig. II), and we quote Professor Palmer's description. "The commonest sites

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for the tumour are around the hip and the elbow. They occur near the scapula, around the shoulder, in the foot, and in the gluteal muscles and they vary infinitely in size and shape. They start as small, discrete, calcified nodules and progress to large and more definite lobulated tumours. Some are lacy, some are linear, and others are solid. They all vary in density, in this respect resembling closely the fragmented and sclerotic epiphysis seen in osteochondritis of the femoral head. They do not affect the joint or the near-by bone except at the elbow. Once seen the appearance is characteristic and is the same at every site. Only the size and shape alter, not the pattern."

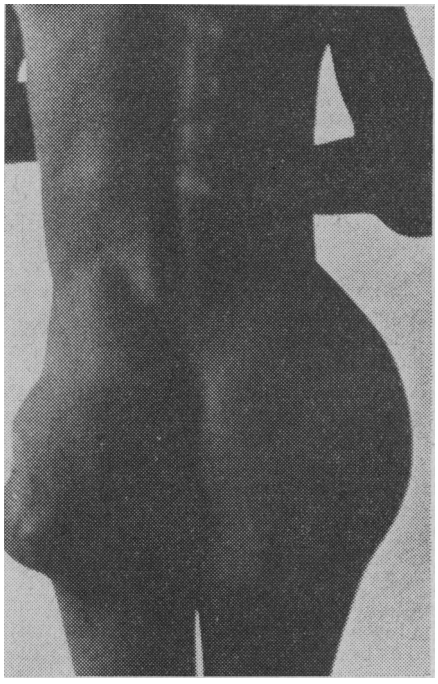

FIG. I.—Case 5. Typical nodules, in this case multiple, seen around the hips and elbows in tumoral calcinosis.

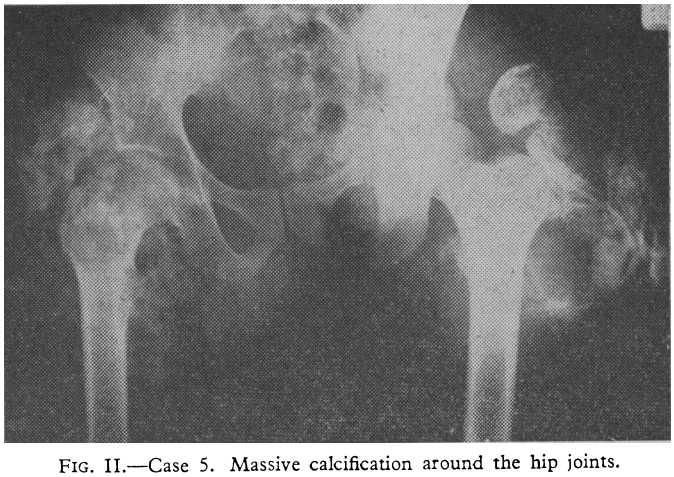

FIG. II.—Case 5. Massive calcification around the hip joints.

When removed the typical tumour is surrounded by dense white fibrous material, and ordinarily is so hard that one needs a saw to cut it across. The cut surface has a honeycomb yellowish-white appearance with some of the "cells" full of a solid calcified material, but from others a chalky white turbid fluid spills out (Special Plate, Fig. 1). This fluid coming from such a tumour is so characteristic that Professor Palmer (personal communication) suggested the correct diagnosis merely from the description in our initial correspondence.

The histological appearances vary somewhat with the stage of the lesion. In a typical case the cysts are surrounded by a dense fibrous capsule which infiltrates and to some extent replaces the adjacent muscle fibres. Those muscle fibres surrounded by the fibrous strands show varying stages of degeneration. A scattering of inflammatory cells is present in this area, mostly lymphocytes, but also with some plasma cells and occasional eosinophils and neutrophils. The cysts vary considerably in size. They are separated by fibrous trabeculae of varying thickness. Some trabeculae are quite dense, but others appear oedematous and vascular. The cysts contain a granular material which is basophilic (H. and E. sections) and positive for calcium (von Kossa stain), and scattered here and there are larger irregularly rounded eosinophilic plaques which are said to be degenerating collagen (Special Plate, Figs. 2 and 3).

The amount of activity differs in various parts of the specimen. In some cysts the lining is merely fibrous tissue, but in others it consists of irregular layers of cells—some with single vesicular nuclei and amphophilic cytoplasm (probably histiocytes); and others with multinucleated giant cells which appear to be aggregates of histiocytes. Some of the giant cells enclose masses of the granular debris, while others surround, in part or wholly, some of the degenerating collagen plaques (Special Plate, Fig. 4). Some of the single histiocytes enclose yellow granules which appear to be haemosiderin. Inflammatory cells are also present in the deeper parts of the lining, adjacent to the fibrous stroma. In one or two cases metastatic nodules of bone formation have been seen in the tumours, lying between the histiocytic cyst lining and the fibrous stroma. The bone seems to be extending inwards to engulf the debris mentioned above, so that small lacunae partly filled with this basophilic material lie surrounded by well-formed bone.

In Case 5, which was the most rapidly growing of all the tumours we have seen, the dense fibrous tissue replacing muscle contained numerous thick-walled arterioles of various sizes, with narrow lumina. In the midst of this dense tissue were rounded oedematous areas containing a cluster of giant cells with foamy cytoplasm. The smallest of these areas showed no necrosis, but in larger ones there was central breakdown with formation of small cysts like those referred to above. It may be that this is the way the larger cysts start. An interesting feature was the presence of extravasated red blood cells in these areas and deposits of yellow pigment, probably haemosiderin. The red cells appeared to be sickled. In some of the other cases abnormal red cells were also seen. This finding is considered to be unrelated to the tumoral calcinosis, as sickle cell and other anaemias are common in Kenya.

Correlation of Data

Out of 19 cases in which the sex was stated 11 were female and 8 male. Ages were not given in most cases. There were two children aged 11 and 12. The remaining 17 were adults. Ages stated varied from 18 to 75.

The duration of the lesion was stated in 12 cases: four were of less than six months' duration, four were two years or less, two were three years, one was indefinite, and one was of many years' duration, but recently had been growing rapidly.

The commonest anatomical location was over the greater trochanter. Here there were 15 tumours, including three cases in which they were bilateral. Four were located in the buttocks, three on the elbows, and one each on wrist and knee. One child had multiple swellings in the thighs and left jaw, and later in the elbow and both buttocks (included in the above listings).

Two of the tumours had skin ulcers over them and three had perforated. All of these were over greater trochanters or hips.

Investigation of the tribal origin of 17 patients revealed eight different tribes—six were Kikuyu, three Kisii, two Luhya, two Meru, one Kipsigis, one Mkamba, one Luo, and one Masai. The regions from which these people came were not accurately pinpointed, but the hospitals which sent in the specimens were

scattered over the west and central parts of Kenya. There were no specimens from northern, north-eastern, or coastal areas or tribes.

Discussion

It is not our intention to discuss the causation of tumoral calcinosis. Our information is limited only to the few remarks on the biopsy form sent in with the specimen, and follow-up is impossible under present circumstances. From the data we have, and it should be realized that we deal almost exclusively with Africans, it appears that various ethnic groups—Hamitic, Nilo-Hamitic, and Bantu—have the disease. There is a slight preponderance of females, which is the opposite of Palmer's (1966) findings, and no obvious age limitation from the second decade onwards. As in the previous series, the sites of tumours are near joints. Unlike the cases reported by Palmer (1966) and Thomson (1966) we had none near the shoulder or scapula, which would cast doubt on the thesis that pressure on certain areas during sleep or resting on the ground or on hard beds predisposed to its location there. However, the great preponderance of tumours in "pressure areas" around the hips, with ulceration and even perforation in some cases, cannot be dismissed as pure chance.

Another point of difference in our series is that we have seen occasional bone formation, so that the condition is not quite "the exact reverse of myositis ossificans" as suggested by Thomson (1966). However, we have no theory to offer regarding its causation.

It is worth mentioning for its negative value that we obtained a sterile specimen from the one case that came to our hospital. No organisms could be grown. At the moment surgical excision is the only effective treatment.

We wish to thank Mr. N. Ahmed, formerly provincial surgeon, Nyanza, and now in Australia, and Mr. J. R. M. Miller, surgical consultant, Kenyatta National Hospital, Nairobi, for their assistance with some of these cases. At Mr. Miller's suggestion Dr. Palmer was consulted and provided the missing clues to the proper diagnosis. Mr. J. A. M. White, senior lecturer, Department of Surgery, University College of Rhodesia, confirmed Professor Palmer's findings.

REFERENCES

Palmer, P. E. S. (1966). *Brit. J. Radiol.*, **39**, 518.
Thomson, J. G. (1966). *Brit. J. Radiol.*, **39**, 526.

Effects of Phenoxybenzamine in Shock due to Myocardial Infarction

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Summary: Treatment of cardiogenic shock with vasodilator drugs has been advocated on the basis of experimental work showing that a fall in peripheral resistance allows the cardiac output to increase without any increase in cardiac work.

Seven patients suffering from shock secondary to myocardial infarction were treated with phenoxybenzamine. In two cases there was dramatic improvement in the signs and symptoms of shock, but in six of the seven cases there were severe adverse effects on respiration, including the development of wheezing and rales and rhonchi.

Introduction

When myocardial infarction is accompanied by hypotension and weak or impalpable peripheral pulses, together with pallor, cyanosis, clouding of consciousness, and oliguria, the mortality is greater than 80% (Epstein and Relman, 1949 ; Cronin *et al.*, 1965). Many therapeutic regimens have been advocated for this state but none has become generally accepted.

Vasopressors are usually considered to be of little value and even harmful (*Lancet*, 1966), though these views are not universally held (Kuhn, 1967), and it has been suggested that vasodilator drugs be tried instead in view of their beneficial effects in experimental cardiogenic shock, in which it was thought that the resulting fall in peripheral resistance allowed increased cardiac output without any increase in cardiac work (Dietzman *et al.*, 1967).

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Reports of the use of phenoxybenzamine in patients with shock due to myocardial infarction are sparse and give few details of its effects (Wilson *et al.*, 1964 ; Pentecost and Mayne, 1968). Our own experience with this drug in such patients is limited. Though we have obtained beneficial results in two patients, our main purpose in this article is to draw attention to hitherto undescribed adverse effects which may prove fatal in some cases.

Patients Studied and Methods

Some details of the seven patients we have treated are given in Table I. The clinical diagnosis of myocardial infarction was substantiated either by diagnostic electrocardiographic (E.C.G.) changes or by suggestive E.C.G. changes accompanied by a rise in serum aspartate aminotransferase activity. Infarction was confirmed at necropsy in four of the six patients who died ; in the other two, who died within 24 hours of the onset, only coronary occlusion was demonstrable.

In all cases a systolic blood pressure of 80 mm. Hg or less was associated with weak or impalpable peripheral pulses, pallor, cold moist extremities with constricted veins, mental confusion, and restlessness. Urine output was 25 ml./hour or less in all, and five were anuric. These signs were present for at least four hours before treatment with phenoxybenzamine was begun and had not improved with standard treatment, including oxygen by face-mask, diuretics, adequate analgesia, and control of arrhythmias. Vasopressors were not used. The prognosis appeared to be very poor and the Peel prognostic index (Peel *et al.*, 1962) confirmed this.