hæmo- and leucopoietic cells in the marrow by the marked proliferation of the macrophage cells, a high proportion of which are parasitized. It is possible that in some cases of kala-azar agranulocytosis is due to severity of infection, the excessive proliferation of the macrophages almost entirely replacing the formative elements in the marrow. Sternal puncture smears of 2 cases (case II and the case reported in 1943) showed a very marked aplasia of the cells of the granulocytic series. Also in both these cases unusually large numbers of parasitized and non-parasitized macrophages were seen. Zia and Forkner (1934) also published photomicrographs of sections of bone marrow showing large number of parasitized macrophages and extreme paucity of the myelocytes and more mature granulocytes.

In the cases where agranulocytosis developed during the course of treatment with pentavalent antimonials the workers in China were of the opinion that antimonials played some part in precipitating an attack of agranulocytosis. This is no doubt possible, though repeated injections of antimony compounds have never been found to possess any significant action on the blood picture of experimental animals by Forkner. The other possibility in such cases is that treatment may either be inadequate in controlling a severe infection or cause a further stimulation and proliferation of the macrophage cells thus leading to a further depression of granulopoiesis. It is not possible just at present to decide either way. But it may be mentioned that the patient, who developed agranulocytosis after receiving about a dozen injections of antimonials, required a second full course of injections of a different antimonial for her clinical cure of kala-azar.

The question whether the pentavalent antimonials should be used or not during agranulocytosis is however not difficult to decide. In untreated cases of kala-azar it is justifiable to administer antimonials, and in the cases where the condition develops during the course of treatment with an antimonial, it is more reasonable to withhold antimonials till the condition subsides, and then start treatment of kala-azar with a different antimony compound.

There is little to discuss about the general supportive measures and symptomatic treatment. Blood transfusion is regarded by some workers as valuable; but unless the patient is severely anæmic, there does not seem to be any indication for this procedure which may prove risky in patients with high temperature of 103° or higher. Chances of hyperpyrexial reactions are not inconsiderable even with blood samples from well-regulated blood banks and when the technique of transfusion is beyond reproach.

Summary and conclusions

Three cases of agranulocytosis complicating kala-azar are reported and the clinical features discussed. It has been found that the usual lesions affecting the mucous membrane of the mouth and the pharynx may be very inconspicuous or even absent in some cases. The high fever that is associated with agranulocytosis persists even when there is no apparent infection anywhere and the slight infections present entirely relieved by penicillin, till about 250 or more neutrophil cells appear in the peripheral blood.

The treatment of this condition is discussed. Penicillin relieves the oral lesions if present and it can prevent secondary infection with a large group of organisms. The well-known leucopoietic agents, pentnucleotide and whole liver extract should be administered in full doses. The specific treatment for kala-azar with pentavalent antimonials should be given in previously untreated cases. But in the cases where agranulocytosis develops during antimony treatment it is preferable to withhold the specific treatment of kala-azar till this complication has been relieved. The treatment should include general supportive measures, *viz,* adequate nourishment and fluid intake, and symptomatic treatment for toxæmia, circulatory failure, etc.

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[*P.S.*—After this paper had been sent for publication one more case of previously untreated kala-azar complicated by agranulocytosis was admitted under my care. The diagnosis was made on clinical grounds and confirmed hæmatologically and by finding leishmania on sternal puncture. The treatment was by a pentavalent antimonial-penicillin—pentnucleotide liver extract—therapy along with general supportive measures. The patient made an uneventful recovery, the high fever persisting till the subsidence of agranulocytosis.—P. C. S. G.]

THE ÆTIOLOGY OF 'PHRYNODERMA'

By C. GOPALAN, M.D.

(*From the Nutrition Clinic and Research Ward, Stanley Hospital, Madras, and Nutrition Research Laboratories, Coonoor*)

A LARGE number of cases of phrynoderma was observed among the patients that attended the Nutrition Clinic. In the present investigation, the following observations were made regarding (*a*) the incidence of phrynoderma and (*b*) the response of the disease to certain lines of treatment.

Incidence

Age and sex.—In the course of the investigation, 116 cases of phrynoderma were observed. Most of these cases belonged to the poor class and a few to the so-called 'lower middle' class.

The distribution of the cases according to sex and age groups is given below :—

	Below 5	5 to 10	10 to 15	15 to 20	Above 20
Males ..	1	12	20	11	7
Females	2	18	28	13	4

It is noteworthy that nearly 70 per cent of the cases were between 5 and 15 years. The incidence in adults was relatively low. A significant feature was the strikingly low incidence, less than 3 per cent, in children below 5 years.

The age and sex incidence of a group of 134 cases of xerophthalmia observed in the course of the investigation was as follows :—

	Below 5	5 to 10	10 to 15	15 to 20	Above 20
Males ..	36	21	9	5	2
Females	28	18	7	5	3

Nearly 50 per cent of cases of xerophthalmia were children below 5 years. Thus, accepted manifestations of vitamin A deficiency were predominantly present in children below 5 years; and it was in this very age group that phrynoderma was particularly rare.

Associated deficiency signs.—Of the 116 cases observed, 4 cases did not show any clinical sign of nutritional deficiency. The others presented obvious signs of malnutrition as shown below :—

	B_2 complex deficiency signs	(1) + xerophthalmia	Xerophthalmia alone
Number of cases of phrynoderma.	94	14	4

Thus in nearly 92 per cent of cases of phrynoderma, clinical evidences of B_2 complex deficiency were present. On the other hand accepted clinical evidence of vitamin A deficiency was present in about 15 per cent of cases of phrynoderma.

The incidence of phrynoderma in a group of 134 cases of xerophthalmia drawn from the Ophthalmic and Nutrition departments was also investigated and is represented below :—

	With phrynoderma unassociated with B_2 complex signs	With phrynoderma associated with B_2 complex signs	Without phrynoderma
Number of cases of xerophthalmia.	4	14	116

Seasonal incidence.—The incidence was high in the colder months of the year. With the coming in of the hot season, there was a distinct decline in the number of cases observed. It may be pointed out that the average attendance at the Nutrition Clinic was nearly the same throughout the period of the investigation.

	Sept.	Oct.	Nov.	Dec.	Jan.	Feb.	March	April	May	June	July
Number of cases	6	11	19	22	24	16	8	3	2	3	2

Treatment

Therapeutic trials were carried out on 37 cases of phrynoderma with six kinds of treatment as indicated in table I.

TABLE I

Treatment	Number of cases of phrynoderma			
	Total	Associated with B complex signs alone	Associated with B complex signs and xerophthalmia	Associated with xerophthalmia alone
1. Vitamin A concentrate ..	5	1	3	1
2. Nicacinamide	4	3	1	..
3. Riboflavin	5	3	2	..
4. Yeast extract	9	6	2	1
5. Linseed oil	6	5	1	..
6. Yeast extract + linseed oil	8	6	2	..

These cases were treated as out-patients so that the hospital diet may not vitiate the results. The patients continued to subsist on their usual diets during the period of treatment and did not get any drug other than that used in the investigation. Treatment on the different lines was carried out for periods ranging from 5 to 6 weeks. To assess the result of the treatment, it was found convenient to 'grade' the cases after treatment as follows (*see* figures, plates I and II).

Grade I—Cases in which there was definitely no improvement.

Grade II—Cases in which the improvement was 'not definite' or 'doubtful'—inconclusive. In this grade are included cases in which the 'eruptions' appeared to have become relatively sparse in places but had not disappeared partly or entirely from any area.

Grade III—Cases in which improvement was definite but not complete. In this grade are included cases in which at the end of treatment the 'eruptions' had disappeared partly or entirely from certain areas and over other areas they had become sparse.

Grade IV—Cases in which improvement was 'complete'. The 'eruptions' had disappeared almost completely leaving behind small circumscribed areas of pigmentation.

The treatment adopted and the response thereto are indicated in table II.

TABLE II

Treatment	Daily dosage	Number of cases	Response			
			Grade I	Grade II	Grade III	Grade IV
Vitamin A concentrate ..	10,000 I.U.*	5	4	1	..	..
Nicacinamide	200 mg.	4	4	..	..	..
Riboflavin	10 mg.	5	3	2	..	..
Yeast extract	4 to 6 drachms	9	..	1	3	5
Linseed oil	1 to 2 ounces	6	..	2	2	2
Yeast extract + linseed oil ..	4 to 6 drachms + 1 ounce of oil.	8	..	..	1	7

*Parenterally in 3 cases and as capsules orally in 2 cases.

Discussion

The vitamin A deficiency hypothesis.—Much of the support for the vitamin A deficiency hypothesis has been derived from the observation of several workers that administration of substances rich in vitamin A—fish liver oils—over prolonged periods has cured the skin disorder. Stannus (1945) has pointed out that the tests employed have generally been not exclusive and control observations have been wanting. 'For many cod liver oil has been synonymous with vitamin A and supplements to the diet have often been made at the same time'. It must be remembered that the fish liver oils used by some workers, and cotton seed oil, groundnut oil, etc., employed by some others as vehicles for the vitamin A concentrate in these therapeutic tests, are all fair sources of fatty acids.

Another point that has to be considered in a number of these therapeutic tests is with regard to their prolonged duration. It has been shown that the incidence of the disease is definitely influenced by seasonal factors and the same observation has been made by several workers. It is a question, however, whether seasonal variation can influence the course of an established case; but the possibility may not be denied. The possible contribution of the seasonal variation to the result of treatment has to be remembered in assessing the value of therapeutic tests spread out over several months.

Several workers including Frazier and Hu (1936), and Frazier, Hu and Chu (1943) have remarked on the lack of correlation between the incidence of phrynoderma and accepted signs of vitamin A deficiency. Frazier and Hu (1931) suggest that the preponderant incidence of phrynoderma in the second decade is related to the development of the pilosebaceous glands occurring round about the pubescent period. If this were so, it would explain the absence of phrynoderma in cases of keratomalacia occurring in infancy and early childhood, but cannot explain either the frequent absence of phrynoderma in older cases of keratomalacia or the frequent absence of keratomalacia in cases of phrynoderma. Hawes (1945) on the other hand suggests that the predominant incidence of phrynoderma in this period may be due to a marked disparity between the carbohydrate intake and fat intake in the diet of the poor in this period which may accentuate a relative deficiency of some fatty acid.

Frazier and Hu (1936), and Lehman and Rapaport (1940), remarking on the absence of xerophthalmia in several cases of phrynoderma, suggest that in the evolution of the clinical signs of vitamin A deficiency, the skin manifestations may precede the ocular signs. Even if this were true, it would not explain the frequent absence of phrynoderma in advanced cases of xerophthalmia. Moreover, Jeghers (1937) and Getz (1944), who attempted to induce vitamin A deficiency in man, found that the very first

manifestations were always ocular. Bloch (1917) and Pillat (1929) who studied the condition of the skin in cases of keratomalacia did not find follicular lesions. Bloch (1917) reported on the other hand 'a dry shrivelled and scaly condition of the skin' and Pillat (1929) described the skin in keratomalacia as 'slaty-grey, wrinkled, dry and scurfy'.

Lehman and Rapaport (1940) point out, in support of the vitamin A deficiency theory, that in 9 cases of phrynoderma in which there was no evidence of xerophthalmia, dark adaptation tests revealed impairment of adaptation. Subclinical defects cannot have the same significance as manifest clinical signs with regard to the ætiology of an associated disorder. Moreover, recent work (Kimble and Gordon, 1939; Morton, 1944; Pollak, 1945) seems to suggest that deficiency of some members of the B complex may also have some relation to the impairment of dark adaptation in some cases.

Rao (1937) concluded from a histopathological study of his cases that in the development of the disorder vitamin A deficiency may probably be an important factor. But Wolbach and Bessey (1942), reviewing the tissue changes, suggest that the disorder 'might be related to riboflavin deficiency rather than A deficiency, as previously concluded from rather inadequate evidence'. Moult (1943) observed lesions closely resembling those of phrynoderma in rats fed on diets deficient in vitamin A. Stannus reveals that the vitamin, in this experiment, was administered in the form of a fish liver oil concentrate of high potency diluted with edible groundnut oil. The introduction of groundnut oil in the experiment would seem to vitiate its value.

The results obtained here do not support the vitamin A deficiency hypothesis. While the dosage of vitamin A used here was larger than that employed by other workers, the duration of treatment was less. However, cases of phrynoderma of comparable severity treated for the same duration on other lines improved definitely. Stannus (1945) and Hawes (1945) also failed to obtain improvement in their cases with vitamin A. Hawes employed vitamin A by injection in large doses 'without observing the slightest effect on the skin' on his cases in the East.

Yeast extract.—The observation that there is correlation between the incidence of phrynoderma and signs of B_2 complex deficiency has also been made by other workers (Platt and Gin, 1935). Nicholls (1933, 1934) reported the presence of neuritis, angular stomatitis and glossitis in several of his cases of phrynoderma.

The frequent presence of signs of B_2 complex deficiency in several cases of phrynoderma and the response of the disease to intensive treatment with yeast extract would suggest that the condition is related to deficiency of some factor in the B_2 complex. This factor is evidently something other than (or more than) nicotinic acid or riboflavin since neither of these by itself yielded the results obtained with yeast extract.

Linseed oil.—The satisfactory result obtained in some cases of phrynoderma with raw linseed oil probably supplies the explanation for some puzzling features regarding phrynoderma. Raw linseed oil is a rich source of unsaturated fatty acids including linoleic and linolenic acids but does not contain appreciable amount of vitamin A. The failure of vitamin A concentrate to appreciably influence the skin condition in cases of phrynoderma and the success obtained in some cases with raw linseed oil would suggest that the curative effect claimed for the fish liver oils is probably due to the fatty acids contained therein.

Yeast extract and linseed oil.—The combined use of yeast extract and linseed oil was more effective than either of these employed separately. It has been demonstrated by several workers (Burr and Burr, 1929; Hogan and Richardson, 1935; Birch, 1938) that there is a definite relationship between the metabolism of certain members of the B_2 complex and that of some unsaturated fatty acids in experimental animals. Birch and György conclude that 'in the absence of a decent supply of certain vitamins of the B_2 group, the animal is unable to make proper use of the fatty acids, or alternatively, in the absence of adequate amounts of unsaturated fatty acids, the animal is unable to utilize these vitamins'.

The lesions reported in these experimental animals, however, do not strictly parallel the lesions in phrynoderma. But it is perhaps possible in the human subjects also, that in the absence of adequate amounts of certain members of the B_2 complex from the diet, there is an imperfect utilization of fatty acids or *vice versa;* that a vicious circle is thus set up, which ultimately leads to the development of the characteristic skin lesions of phrynoderma. If this were so, one may expect to correct the disorder by supplying either the fatty acids or the members of the B_2 complex, but the results are likely to be better if both these substances are used in combination. The observations made in this investigation seem to bear out this expectation.

Summary and conclusions

1. One hundred and sixteen cases of phrynoderma were studied and the response of 37 cases to six different lines of treatment was investigated.

2. The results of the investigations have been discussed and the vitamin A deficiency hypothesis has been examined.

3. The suggestion has been advanced that phrynoderma may be due to related deficiencies of certain members of the B_2 complex and fatty acids.

I am grateful to the Superintendent and staff of Stanley Hospital, Madras, for the facilities extended to me for the conduct of this investigation.

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EXPLANATION OF ILLUSTRATIONS

1-*a* and *b* .. A case of phrynoderma before treatment.
2-*a* and *b* .. The same case after 6 weeks of treatment with pure raw linseed oil. The 'eruptions' have mostly disappeared but small cirumscribed areas of pigmentation marking their sites still remain.
3, 4 and 5 .. Deficiency signs associated with phrynoderma.
3-*a* .. Angular stomatitis in a case of phrynoderma. The conjunctivæ appear bright and clear.
3-*b* .. Skin condition of the case shown in 3-*a*.
4-*a* .. Shows angular stomatitis with acneform comedones on the face. Conjunctivæ appear bright and clear.
4-*b* .. Skin condition of the case shown in 4-*a*.
5-*a* .. Angular stomatitis and glossitis in a case of phrynoderma. The picture shows the patient much darker than she actually was, the conjunctiva therefore appears brownish but actually there was no evidence of xerophthalmia.
5-*b* and *c* .. Skin condition of 5-*a* above.

ANEURYSM OF THE PULMONARY ARTERY WITH PATENT DUCTUS ARTERIOSUS

By R. SUBRAMANIAM, B.SC., M.D. (Madras), M.R.C.P. (Lond.)

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ANEURYSM of the pulmonary artery is a rare condition. In the Indian literature, the case reported by Rogers (1908) of a dilatation of the artery with atheroma seems to be the only case. Scott (1934) was able to collect 89 cases from literature between the periods of 1836 and 1934. Wahl and Gard (1931) reported a case of aneurysm of the pulmonary artery in a girl aged 19. In this case symptoms dated from birth. Pre-operative diagnosis was mitral stenosis and mediastinal tumour, no pulsation on screen. Hæmoptysis was present, blood Wassermann was negative. E.C.G. showed right side preponderance. *X*-ray therapy had no effect on tumour masses. The case was observed for 27 months. Definite signs of heart failure at rest developed with clubbing of the fingers. Bulging of the manubrial area increased and the patient complained of a dull pain in the same area and hæmoptysis with constant cough. The case was operated upon, and the tumour exposed and incised. Blood gushed out and the patient died. Autopsy showed wide open patent foramen ovale. Pulmonary artery and the two branches up to the point of entry into the lung were greatly dilated. Wilkinson (1940) reported a case of aneurysmal dilatation in a girl of 10, with rupture of the pulmonary aneurysm into the pericardium. Holmes (1944) has reported a case of patent ductus arteriosus associated with pulmonary aneurysms and infective endocarditis.

Ætiology.—While, undoubtedly, the commonest cause of aortic aneurysm is syphilis, it is not so in the case of pulmonary artery aneurysm. Diseases of the pulmonary artery and its branches are of manifold ætiology and the different age groups are affected almost equally.

1. Aneurysm of the pulmonary artery seems to be most often congenital in origin. Congenital dilatation of the pulmonary artery is associated with other congenital defects, as patent ductus arteriosus, and patent inter-arterial (the commonest) or inter-ventricular septum. The pulmonary valves are in most cases bicuspid. Trauma, as by a bullet wound of the chest, has caused aneurysm. Rupture of the dilated aneurysm has been observed in a few cases. It is noteworthy that in nearly all cases of patent ductus arteriosus, the pulmonary artery is dilated to some extent. Aneurysm of the patent ductus arteriosus has also been recorded.

2. Less often it is associated with syphilis. Warthin has demonstrated the spirochæte in the aneurysmal wall in one case.

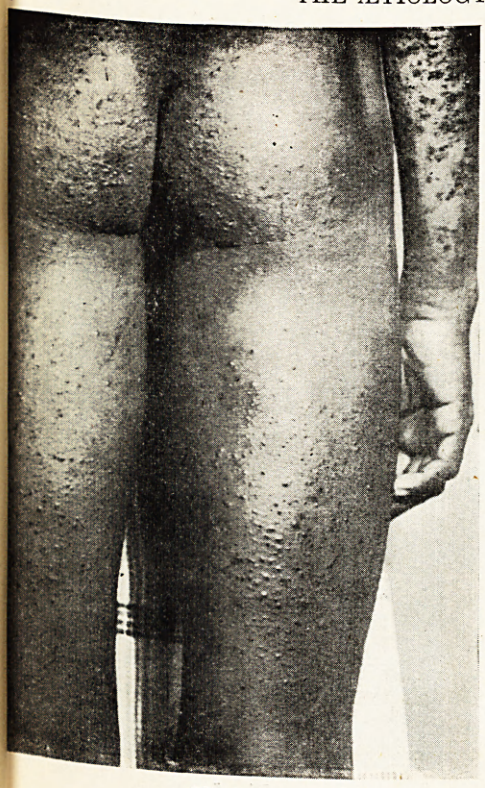

Fig. 1*a*.

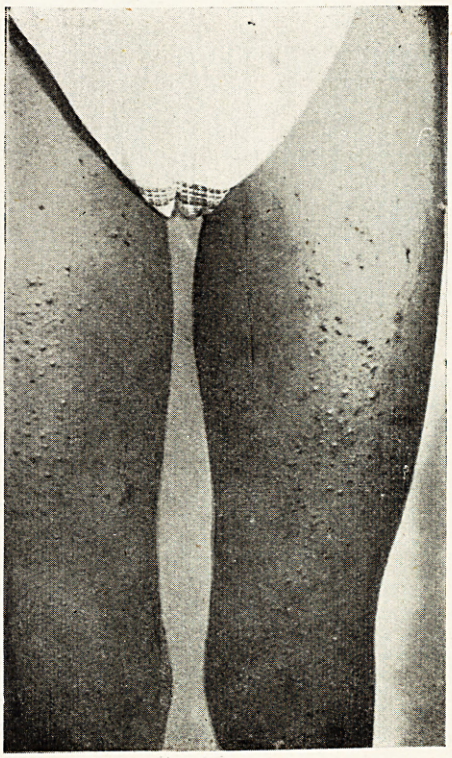

Fig. 1*b*.

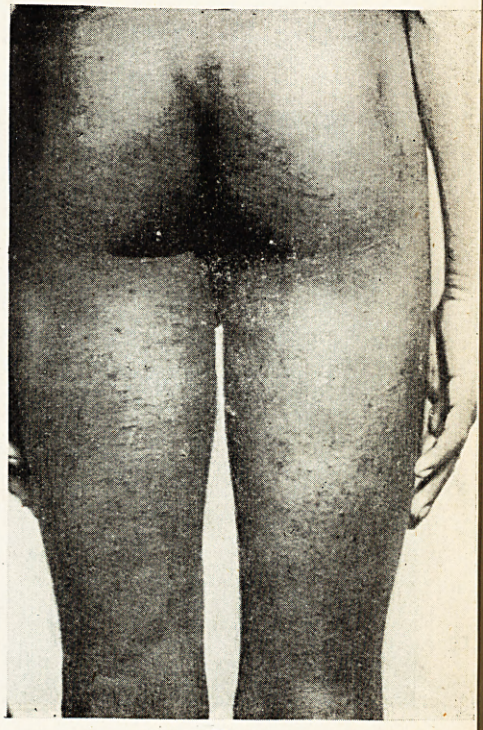

Fig. 2*a*.

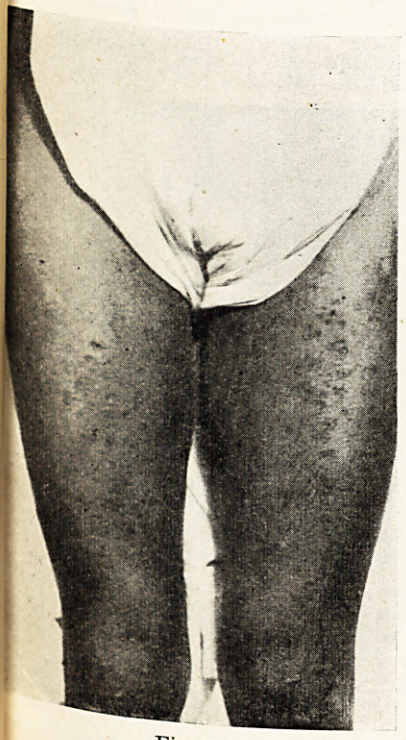

Fig. 2*b*.

Fig. 3*a*.

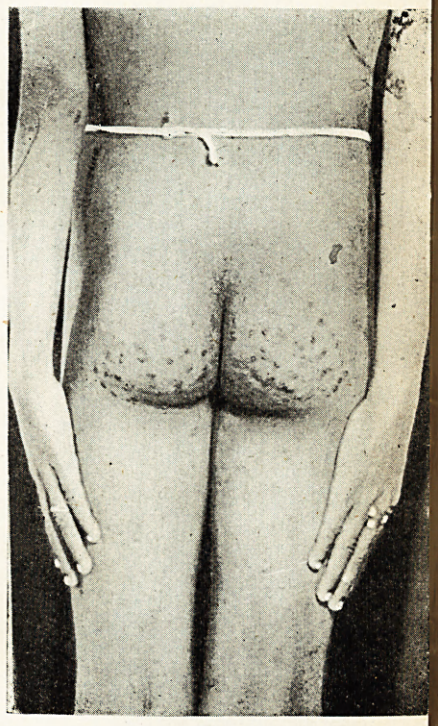

Fig. 3*b*.

PLATE II

THE ÆTIOLOGY OF 'PHRYNODERMA' : C. GOPALAN. (O. A.) PAGE 16

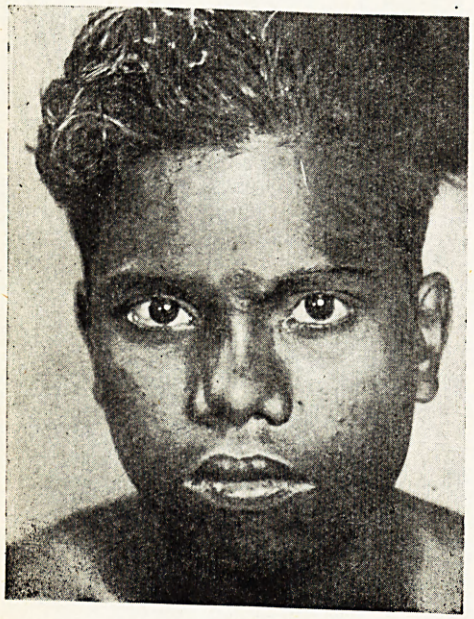

Fig. 4*a*.

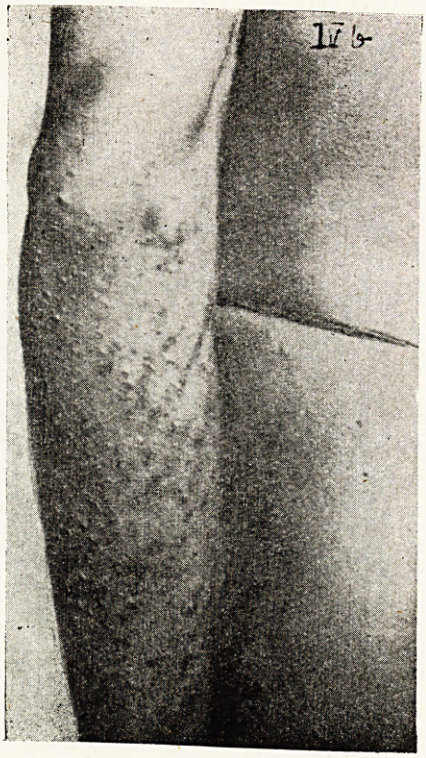

Fig. 4*b*.

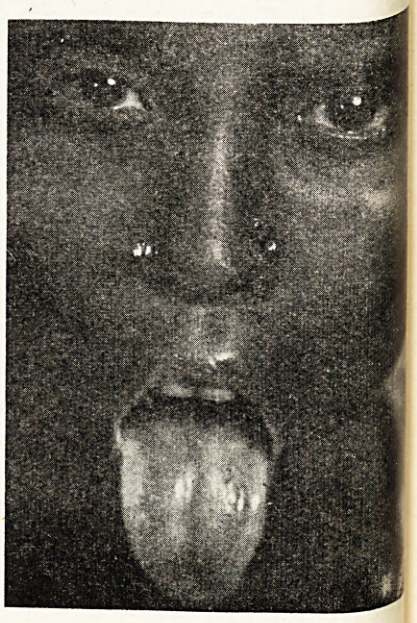

Fig. 5*a*.

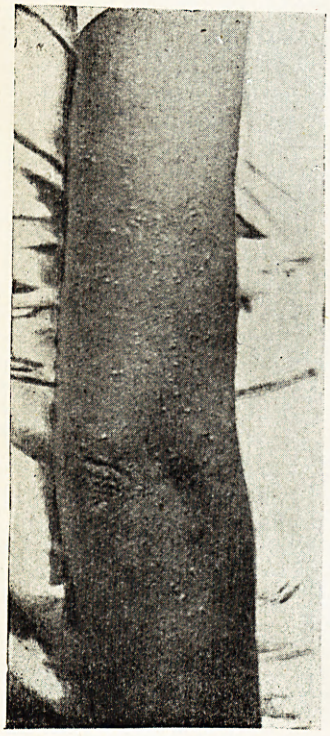

Fig. 5*b*.

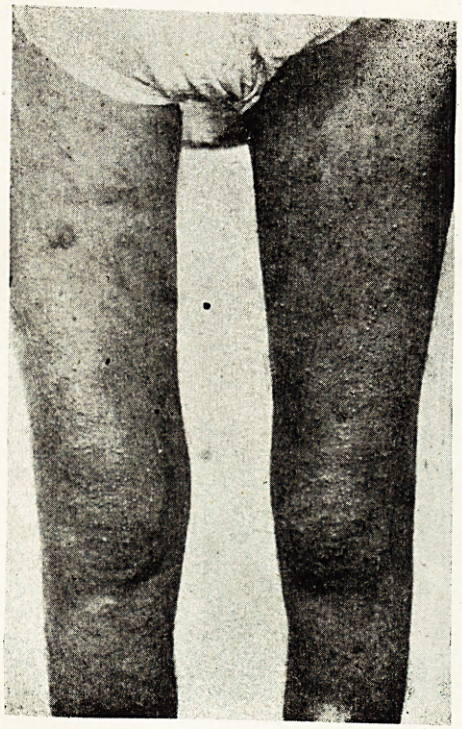

Fig. 5*c*.

OSTEO-SARCOMA OF CERVICAL SPINE
I. AHMAD. (M. H. P.) PAGE 23

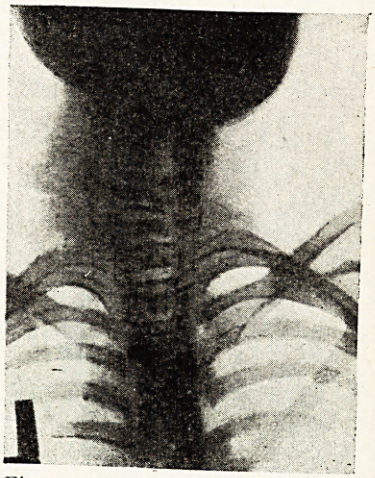

Figure showing calcifying tumour growing from and destroying the left half of the 4th, 5th and 6th cervical vertebræ.