RHINOPHYCOMYCOSIS

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In 1956 Lie Kian Joe and others described "a new disease", a slowly growing painless subcutaneous granuloma of the limbs and trunk caused by a fungus of the class Phycomycetes and seen at that time only in Indonesian children between 5 and 14 years old. They called it Subcutaneous Phycomycosis. In 1960, W. St. C. Symmers reported the first case seen in England, in a Dutch girl who had recently gone to England after living in Indonesia. This disease was later seen in the Sudan, East Africa and Nigeria presenting the same clinical and histological features as those so graphically described by Joe and his co-workers. The first two Otolaryngological manifestations of this disease were seen in the E.N.T. department of this hospital in 1959, but the absence of a Mycologist and unfamiliarity with the histology of this granuloma made diagnosis impossible until 1962, when a typical infection in the lower limb of a Nigerian child was seen and diagnosed for the first time, and shortly after this two patients with lesions in the upper respiratory tract were seen within a week of each other. Diagnosis was based solely on the recently recognized histo-pathology, but after studying this in conjunction with the observed clinical features exhibited by the infection in this area, two further cases were diagnosed clinically within the next four months, a diagnosis of the first two cases of 1959 was made, and a review was started of about six other suspected cases seen since then. A resumé of the descriptive reports of subcutaneous phycomycosis given by Authors in Indonesia, the Sudan, East Africa and Nigeria would at this stage prove a useful background "theme" to the discussion of the upper respiratory tract "variations" which are in this paper referred to as Rhinophycomycosis. These variations refer only to phycomycotic lesions of the upper respiratory tract and its immediate precincts, which present the identical histopathological picture as that seen in the subcutaneous phycomycosis.

Description of Subcutaneous Phycomycosis

The lesion occurs on the trunk and limbs. It begins as a painless nodule between the corium and subcutaneous fatty tissue, grows slowly and intermittently becoming, after several months, a large very firm smooth or lobulated mass with palpably distinct edges by means of which the tumour may sometimes be "lifted off" the deeper tissues over which it is

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very mobile. It grows into and replaces some of the fatty tissues, islands of which may often be seen on its cut surface. On the rare occasions when muscle is affected, there is usually local necrosis at the point of invasion without any attempt at further spread into it; there is however one report of extensive hyaline degeneration of the affected muscle. The skin may be normal, smooth or scaly, œdematous or discoloured, with or without superficial ulcers depending on the length of the history and the size of the tumour. The lesion tends to be single rather than multiple, sometimes showing signs of healing at one edge while actively growing at another, but after a long chronic course spontaneous regression occurs. With medical treatment the course of the disease tends to be shortened. All patients have been otherwise very well and have been able to continue their normal daily routine, and no fatal result has so far been reported.

Ætiology

The organisms responsible for the infection are fungi belonging to the large class Phycomycetes, which includes the genera Rhizopus, Absidia, Mucor and Basidiobolus. Of these the organism isolated and cultured in three cases by Joe and others has been a species of the genus Basidiobolus; though isolation and culture have always been difficult and sometimes impossible the histology of the lesion is so characteristic and peculiar to the family of fungi to which this organism belongs that the histological picture can be taken as diagnostic even when no organisms can be isolated. The mode of infection is not known and though trauma is considered to be a likely starting point there has been no history of trauma in any case; there has also been no history of previous debilitating disease.

Histology

There are areas of cellular infitration consisting mainly of eosinophils and histiocytes, one or the other type predominating in different parts of the field. Lymphocytes and plasma cells are also present. Few micro-abscesses with neutrophil cells predominating, and some pseudotubercles with multinucleated giant cells formed by the fusion of histiocytes are also to be found. Where the lesion merges with the dermis, round cells and eosinophils form collars around blood vessels or collect in atrophic sweat and sebaceous glands and hair follicles. Careful search is usually needed to find the straight or occasionally branched hyphae surrounded by a smudgy eosinophilic band of variable thickness and referred to by Joe *et al.*, as granular eosinophilic tissue necrosis, the origin of which is still debated. Around them as around the micro-abscesses there is often, but not always pallisading of histiocytes. Hyphae may be found in some micro-abscesses but appear to be in various stages of degeneration. There is also a characteristic negative finding, the hyphae never grow into the lumen of blood vessels, and though Joe *et alia* claim that they do not

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even grow into the walls, Lynch and Husband (1962) describe penetration into the walls, but not into the lumen, of some vessels, by the fungus in the case seen in the Sudan; this penetration was said to be associated with endarteritis obliterans of the vessel concerned. Vascular spread never occurs. Fibroblasts and fibrous tissue are seen in variable amounts in different parts of the field and may be the only feature in healing areas.

Description of Rhinophycomycosis

All patients have been adults between 18 and 35 years, with a history of 6 to 18 months' nasal obstruction, progressive swelling over the nose and later in the cheek and the upper lip. The swelling over the nose is in the bony or movable part Fig 1, and there may sometimes be apparently

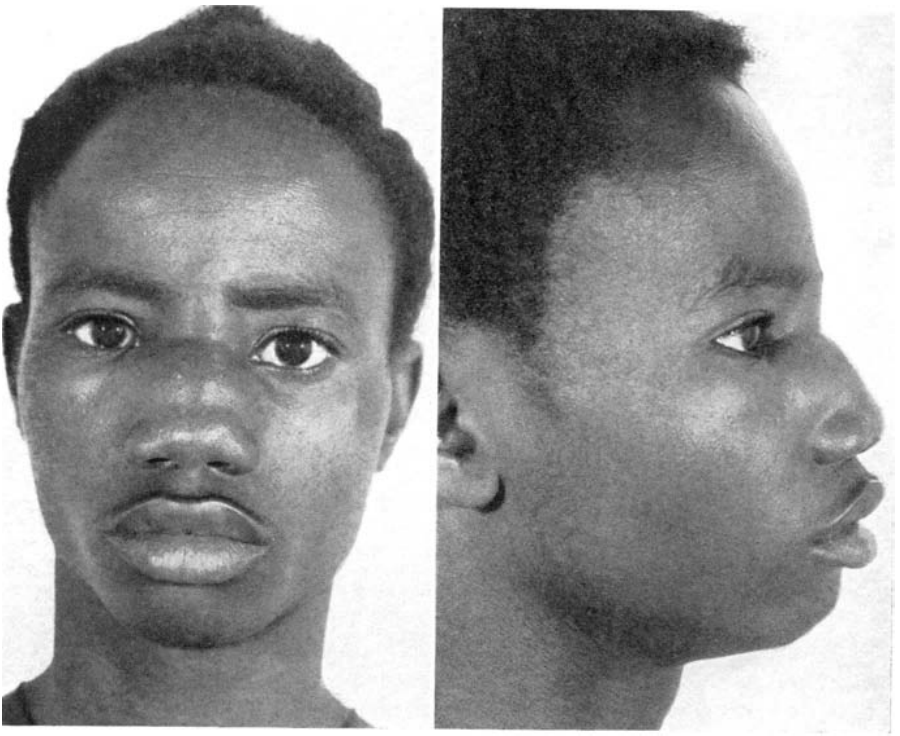


FIG. 1.

The lesion can be seen on the bony part of the nose. There is an early one over the glabella. Diagnosis was confirmed by biopsy taken from the dorsum. This is one of the cases referred to in the fourth column of Table I.

isolated swellings over the glabella, in the lower lid and nasolabial fold (Figs. 2 and 3). Lesions occur in the palate and pharynx. There has never been any history of previous severe illness and the patients have all

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said that they felt perfectly well otherwise, there is never any pain, tenderness or epistaxis.

Compared with subcutaneous phycomycosis, none of the tumours approached the sizes described, the skin over them appeared quite normal except for slight stretching, the findings on palpation were as previously described except that mobility of tumour over deeper tissues was comparatively less, being least on the dorsum and not at all on the movable

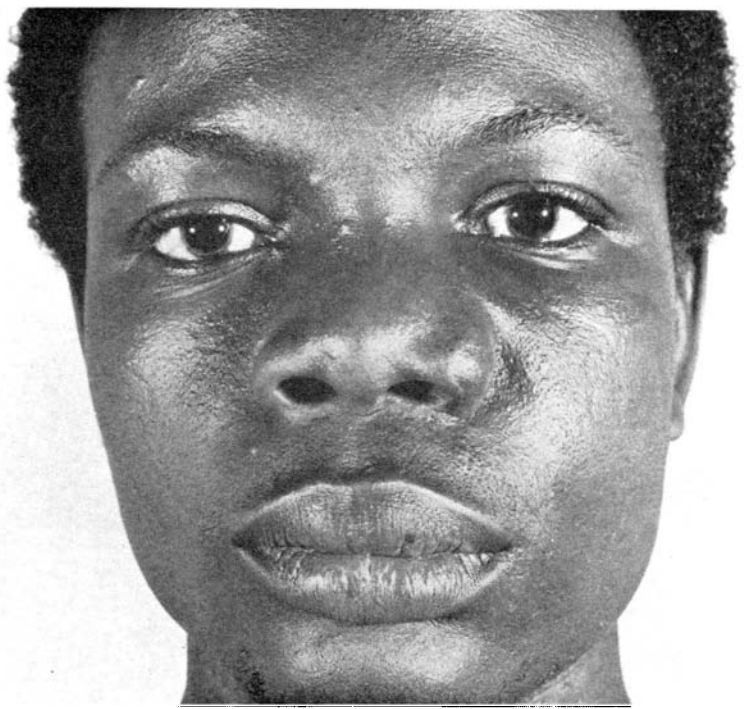


FIG. 2.

Case II. Referred to as J.N. 77631 in Table I. Shows the swelling of the left ala extending on to the cheek and spreading down to the upper lip. Swelling within the vestibule can just be seen.

part of the nose. Other peculiar features of the lesion found on examination or at operation were as follows: (*a*) Lesions in the nose and antra were naturally submucous and not subcutaneous, and in these sites as in the pharynx and palate the lamina propria substituted for the subcutaneous fatty layer; "mucosa" was therefore not movable over the tumours which in turn were hardly movable over deeper tissues. The deep surface of the lip behaved like mucosa in appearing to be "adherent" to the lesions. (*b*) As the facial muscles lay within the subcutaneous fatty tissues and the lesions grew from a deeper plane they tended to spread within the deeper portion of the subcutaneous fat and were therefore, in the face, deep to

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the muscle layer and not superficial to it as in the trunk and limbs. In spite of this the muscles were clinically not affected. (*c*) In spreading from the nasal cavity the lesion travels through and widens the interosseous sutures and foramina. If therefore it emerges through more than one suture the appearance of more than one tumour is simulated. (*d*) There seemed to be a limit beyond which the lesion would not spread outwards in the face in any direction.

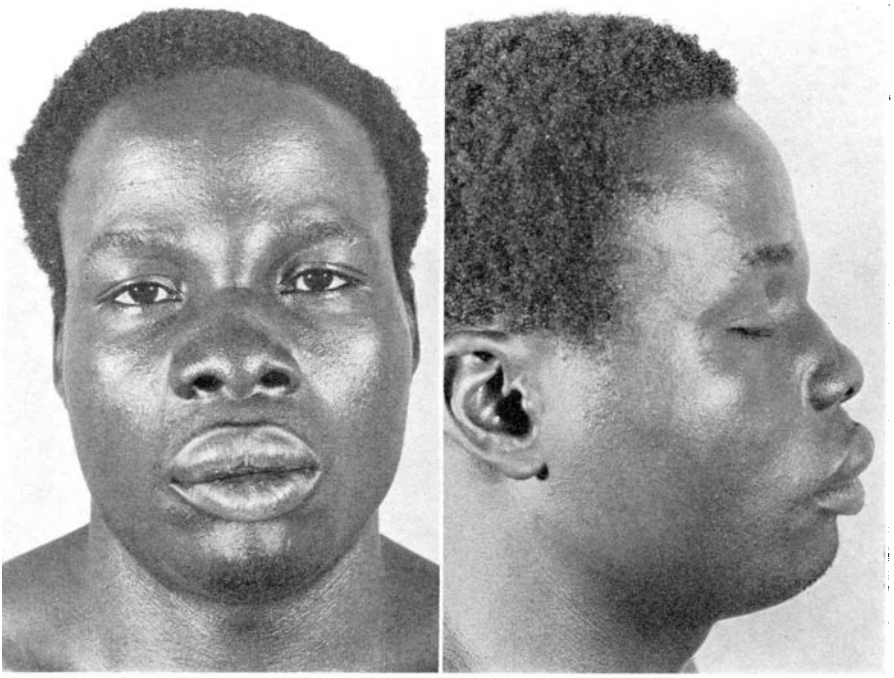


FIG. 3.

Case III referred to in Table I as J.O. 82306. This man has swellings of his right cheek, dorsum of the nose and the upper lip and glabella. This picture was taken after the first operation and though it shows thickening of the upper lip and cheek these are about half the size they reached six weeks later when the second operation was undertaken.

The tumours removed were creamy coloured and tough. In spite of their clinically distinct edges no capsule or definite tumour boundaries could be found. Histologically the pictures were identical with subcutaneous phycomycosis (Figs. 4–6) and like it, cultures were so difficult to obtain, that there was only one successful culture in the series. Pathologist's summary on the sections of all the cases reported in this paper was as follows: "The histological appearance, which was similar in all the cases, was that of a granulomatous reaction characterized by the presence of numerous eosinophils with formation of micro-abscesses in some places. In other places the inflammatory changes were of a more

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chronic type and groups of multinucleate giant cells were seen. There were many scattered collections of eosinophilic granular necrotic substance. In the centres of some of these collections hyphae could be seen. In some places the granular eosinophilic substance was surrounded by palisades of histocytes. The hyphae stained red by the periodic acid-Schiff method.



FIG. 4.

Section showing Hypha surrounded by necrotic substance with diffuse chronic inflammation in the surrounding tissue. Biopsy taken from Case III. Hæmatoxylin and eosin, × 180.

X-rays of the sinuses showed opacity of the antrum and a soft tissue opacity in front of the nose or antrum. No bony erosion was ever shown —a fact that was confirmed at operation in all cases.

Blood counts, chemistry and culture showed no evidence of any disease, nor of adverse reaction to the infection. The complement fixation test used in Indonesia in suspected cases was not practicable here.

Operative Treatment

At first attempts were made to remove as much of the tumour as possible, but after some knowledge of the nature and prognosis of the

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disease was gained, surgical intervention was limited to relieving obstruction, improving cosmetic appearance and obtaining enough material for a satisfactory diagnosis. Approach to various lesions was naturally planned to avoid external scars, and this was practicable except for lesions on the dorsum and the glabella. Lesions in the pharynx were removed per os using the Boyle Davis gag, since lateral pharyngotomy

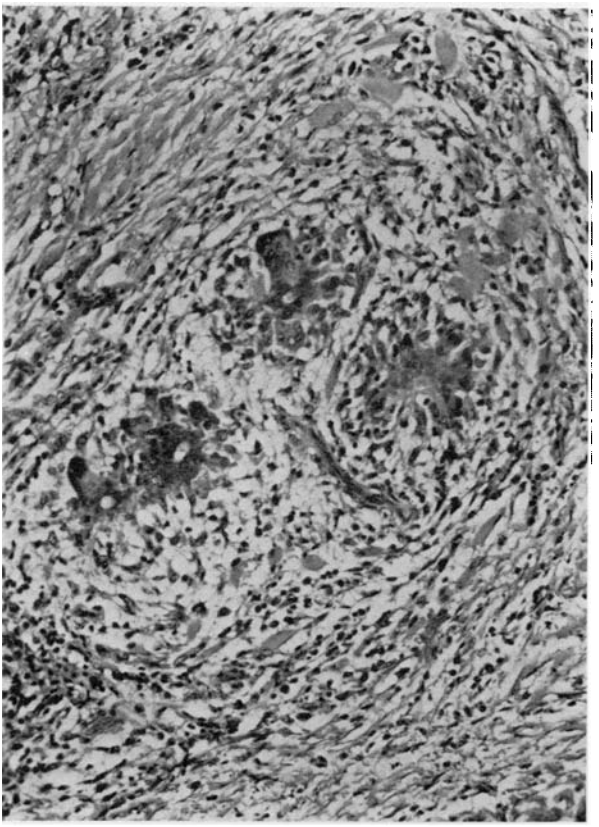


FIG. 5.

Biopsy taken from lip of Case III. Epithelioid cells are arranged in palisades around necrotic eosinophilic granular substances with hyphæ in the centre. Hæmatoxylin and eosin × 160.

was considered too severe for a lesion of this nature and prognosis. The anatomy of the ala nasae precluded operative intervention there since it seemed impossible to distinguish between tumour and the nasal fibrocartilage.

Case Reports

The clinical features of the disease just described are based on the findings in all the cases seen since 1959, but only the three most recent

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cases will be described here. The adjoining table gives a brief comparative summary of their clinical feature (Table I).

Case I. The external swellings here were less prominent than in the other cases. The lesions tended to spread backwards into the pharynx and downwards into the hard palate. He had three operations, the first

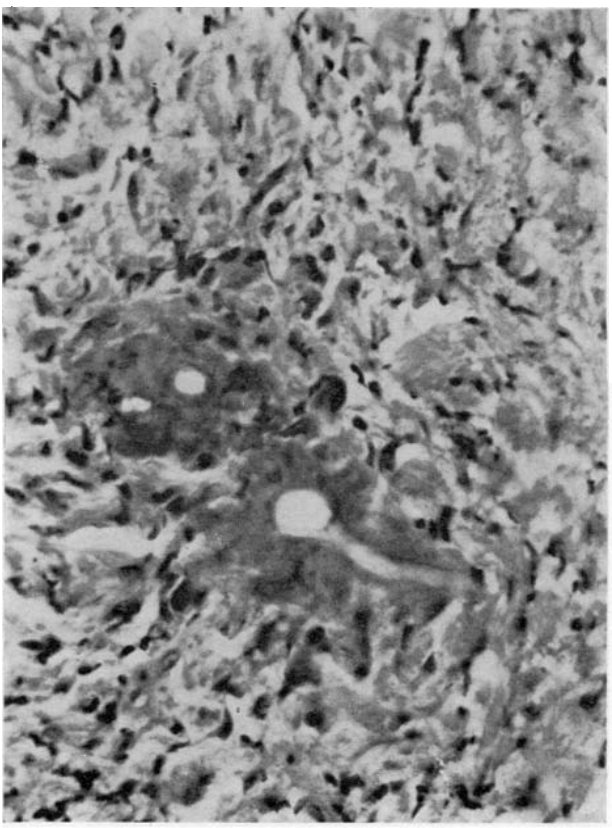


FIG. 6.

Biopsy taken from Case I, shows hypha in micro-abscesses. Hæmatoxylin and eosin × 400.

for biopsy and relief of nasal obstruction, the second 4 weeks later for removal of a tonsil grossly enlarged by the tumour and the third 2 months later for relief of pharyngo-laryngeal obstruction caused by two thick longitudinal masses extending from naso-pharynx down to pyriform fossa. The tumours were tougher and showed a greater proportion of fibrous tissue at successive operations, probably a sign of resolution caused or accelerated by the potassium iodide administered.

Case II. Fig. 2. The lesions here were mainly in the cheek and lip. The nasal obstruction was complete on one side only and after surgical relief there was only partial recurrence and there was no evidence of

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TABLE I.

CASES OF RHINOPHYCOMYCOSIS.

Patient Hosp. No.	O.Y. No. 77205	J.N. 77631 (Fig. 2)	J.O. 82306 (Fig. 3)	Three other cases under review
Sex Age	Male 19 years	Male 26 years	Male 30 years	Males Ages 18–25 years
Occupation	Farmer	Prison Warder	School Teacher	Various
Date first seen	9.1.62	18.1.62	3.4.62	1960 and 1961
General health	Good	Good	Good	Good
Symptoms				
Nasal obstruction	(R) complete (L) partial 6 months	(L) complete 6 months (R) complete 1 month	(R) complete 9 months with catarrh	Moderate — complete unilat.
Dysphagia	Slight at first	—	—	—
Naso-labial fold	Swelling 5–6 months	6 months swelling	7 months swelling	3–7 months swelling
Swelling of cheek	+ 4 months	+ + 6 months	+ + 6 months	} 3–9 months
Swelling of Ala	+ 5–6 months	+ 4 months	+ + + 4 months	
Swelling upper lip	+ 3 months	+ 4 months	+ + 3 months	
Dorsum of nose	+ 3 months	—	+ + 6 months	All three cases
Glabella	—	—	+ + 4 months	2 cases
Palate	4 nodules in (R) side	—	—	—
Oropharynx	(R) tonsil + 3 months later post. phar. wall tumours down to pyriform fossa 4 months after 1st visit	—	—	—
Bleeding	—	—	—	—
History of trauma	—	—	—	—
Findings				
Nasophar. mass	+ +	+		One case
Blood and biochem. investigation	No abnormality	No abnormality	+ No abnormality	No abnormality
X-rays	No bony destruction	No bony destruction	No bony destruction	No bony destruction
Progress	Slow	Very good	Slow	Variable

any attempt to spread beyond the naso-pharynx. He complained of headache and X-rays showed opacity of the one antrum and a soft tissue shadow outside his maxilla and nose. By a combination of the intranasal and Caldwell Luc approaches, the nasal and antral masses were removed, and the anterior ethmoidal cells were cleared out establishing satisfactory patency of the fronto-nasal duct. Five weeks later gross enlargement of the upper lip and cheek necessitated a second operation at which, through two extensive incisions in the sublabial and buccal sulci the labial mass was completely removed—as far as one could see and feel—and the tumour of the cheek was removed as far as practicable. The swelling of the ala nasi had by now completely disappeared.

Case III. Fig. 3. This patient, who alone gave a history of nasal "catarrh" as well as of a slowly progressive obstruction, came to hospital because of the swellings of the upper lip and right cheek, and two isolated ones on the dorsum of the nose and on the glabella. Unlike the others his unilateral obstruction became complete long after the tumours had appeared on the face. That on the cheek extended up to the lower orbital margin and inwards very close to the inner canthus. As usual the first operation was for the relief of nasal obstruction and for biopsy (Fig. 4). Six weeks later the increase in size of the tumours of the cheek and to a less extent that of the lip necessitated a "cosmetic" operation, tissue being sent again for histology to observe the reaction to medical treatment with potassium iodide.

Medical Treatment

In view of the success claimed for potassium iodide by Joe and other authors, and the apparent ineffectiveness of systemic fungicides Griseofulvin, Nystantin and Mycostantin, a mixture containing 10 grains of Pot. Iodid. in the half ounce was given in doses of $\frac{1}{2}$ oz. four times a day. The dangerous side effects of amphoterycin B did not warrant its trial at this stage. Treatment will naturally have to be modified according to results after a few months' trial.

Discussion

Since Cohnheim's report of pulmonary mucormucosis in man in 1865, there have been other reports of the infection in the viscera of the abdomen, thorax, orbit and cranium, as well as in the larynx and the ear. The most fulminating is the intracranial type of lesion. This Dwyer calls Rhinomucormycosis, because it starts in the paranasal sinuses and spreads rapidly into the orbit and thence into the brain. His report of 15 deaths out of 17 cases shows it also to have the worst prognosis. The name Phycomycosis was recommended by Joe *et al.* to include infections by the families of Phycomyctes namely Mucoraceae, Mortierellaceae and Entomophthoraceae. These authors have shown that the organism

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responsible for their cases is the Basidiobolus ranarum which belongs to the last named family. Since this is the only family with produces lesions with the identical characteristic histological picture described earlier, it is logical to assume that the organism responsible for Rhinophycomycosis belongs to it; but as the apparent affinity for, and the restriction to, the upper respiratory tract and its immediate precincts seem to contrast with the anatomical and physiological needs or preferences of the *B. ranarum*, it might be inferred that a different species certainly, if not a different genus is responsible, but its identification will have to wait till the services of a Mycologist are available.

It has been suggested that the name Mucormycosis be used only for lesions caused by Mucor or the family Mucoraceae. These lesions which feature ulcers, sloughs, hæmorrhages, thromboses and necroses, as well as the usual general reactions to an acute infection occur in patients already suffering from some debilitating disease, usually diabetes, but may be anæmia, kwashiokor, leukæmia or some malignant disease. The striking features in the histology here are infarcts, necroses, abscesses and numerous hyphae some of which grow into or within the lumen of blood vessels, blocking or being disseminated by them. Furthermore the cellular reaction (unlike that seen in the subcutaneous disease) is more predominantly neutrophylic. From this broad general picture there is obviously no similarity between Dwyer's Rhinomucormycosis (or mucormycosis of other viscera) and the lesions being discussed in this paper and called Rhinophycomycosis. A comparison of the phycomycoses is given in Table II.

The Phycomycetes are widely distributed in nature. They are seen as domestic and laboratory contaminants, also in certain insects and insectivorous animals such as frogs, lizards, chameleons, ghekos, etc. They have also been grown from human fæces and nasal swabs taken from people who have never suffered from the disease. In culture they have large branching cœnocytic (non-septate) hyphae with an average diameter of 8–12 μ. In sections branching is uncommon, and hyphae may be empty or contain purple staining granular cytoplasm; when they appear distorted or collapsed they are considered to represent dead or degenerating organisms. Biological characteristics are without the scope of this paper and beyond the knowledge of its author. They will therefore not be considered.

The route of infection of Rhinophycomycosis seems to be through the anterior nasal mucosa. Since the organisms are normally commensals in this area it is possible that in a healthy person, trauma, direct implantation by one of the fungus carrying insects, or a purely locally lowered physiological state due to certain infections or to infestation by other parasites such as thread worm ova etc., may create the conditions needed by the fungus to change from a commensal to a pathogen.

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TABLE II.

Comparison of the Phycomycoses.

	Subcutaneous Phycomycosis	Rhinophycomycosis	Mucormycosis
First cases seen or reported	*1956* In Indonesia	In Nigeria *1959*	*1860 or ?1843* In Europe and America.
Age group	5–14 years	18–35 years	3–80 years
General state of health	Good	Good	Poor. Debilitating disease present Diabetes commonest.
Course of the disease	Slow chronic intermittent growth	Slow chronic intermittent growth	Relatively short often fulminant.
Type of lesion	Very large tumour: size limited by length of history. Skin covering usually devitalized.	Much smaller tumour limited ? by facial muscle. Skin and mucosal covering stretched but healthy	Tumour Necrosis, Hæmorrhages. Thromboses. Function of viscus permanently affected.
Site involved	Trunk, limbs and scrotum.	U.R. tract, pharynx, face and lips	Viscera of thorax, abdo, head and neck. In Rhinomucormucosis paranasal sinuses orbit and brain involved
Spread	In subcut. fatty layer. Remains superf. to muscles. No vascular involvement or spread	Submucous planes. In face subcut. fat deep to muscles. No vascular involvement or spread	No limitation to tissue plane. Spreads by growth and destruction: Vascular thromboses and dissemination.
Glands	Not involved	Not involved	Usually affected.
General effect on patient	Not incapacitating	Not incapacitating until nasal or Pharyngeal obstruction becomes severe.	Existing incapacity aggravated. Visceral impairment worsens condition
Prognosis	Good. Eventual spont. recovery, speeded up by medical treatment	Good. Spont. recovery ? speeded up by medical treatment	Poor. Results depend on underlying disease. Cranial type worst.
Histological features	Characteristic. Diagnostic Eosinophil. Cellular reaction few hyphae—no intravascular growth.	Characteristic. Diagnostic Eosinophil. Cellular reaction few hyphae—no intravascular growth.	Acute inflam. reaction, infarcts, thromboses, abscesses. Hyphae + + intravascular growth
Organisms found or suspected	*Genus* Basidiobolus	*Genus* ? Basidiobolus	*Genus* Mucor, Absidia, Rhizopus
Culture of organism	Difficult	Difficult—one successful growth only	Much easier growth

The lesions in the face are not necessarily an overspill from a completely blocked nasal airway since it has been seen in some cases, fourth column Table I, that facial lesions have been present without any marked nasal obstruction, and the extent of facial swelling has borne no relation to the degree of intra-nasal growth. In every case, however, there has always been an obvious intra-nasal "tumour". Any suture or foramen is a potential route of spread outwards from the nasal cavity (Fig. 7). It

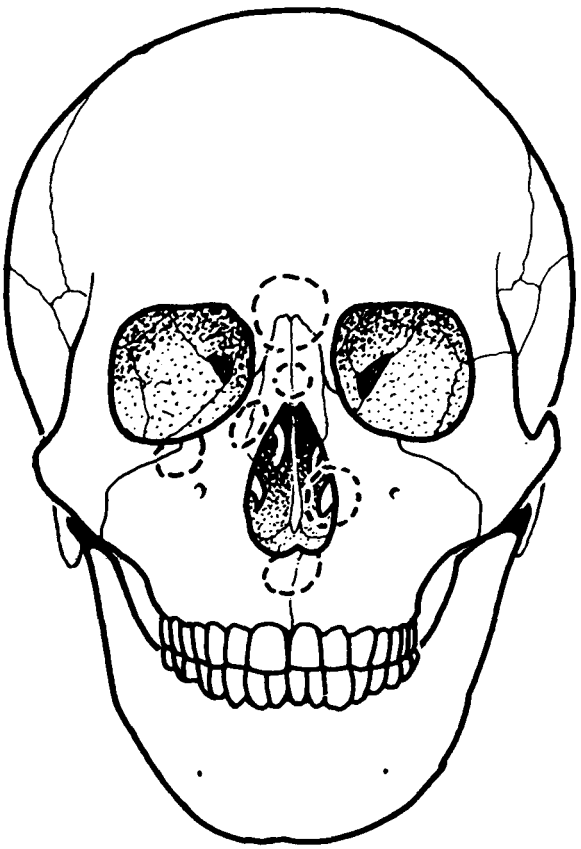


FIG. 7.

The dotted circles in this diagram represent the sites through which "tumours" on the nose and face were found at operation to communicate with lesions in the nasal cavity. In one case a tumour in the right lower lid seemed to have spread from the antrum. At all these points suture lines were visibly widened.

would appear that the facial muscles, probably by being anterior to the tumours, may have some restraining influence on their size and even on the extent to which they may spread laterally.

The general impression formed from all the cases seen since 1959 is that the disease is a sub-mucous phycomycosis of the upper respiratory

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tract in which the lamina propria corresponding to the subcutaneous fatty layer of the body surface is chosen by the fungus as the layer in which to spread, but on entering the face and lips reverts to its form by remaining in the fatty layer. Here, however, its position in relation to the facial muscles probably acts as a restraining influence on its growth both outwards and in thickness. It would also appear that the facial tumours show a greater tendency to fibrosis than those in the upper respiratory tract and as a result biopsies taken from facial lesions may give the impression of infected fibroma, or chronic inflammatory tissue with fibrosis. This has probably been responsible for a number of cases being missed in the past or being mistaken for one of the many "tumours" seen in tropical otolaryngology.

Differential diagnosis. This lies between simple tumours of the (*a*) nose and maxilla including adamantinomata and epulis, as well as fibro-osseous dysplasias and dental cysts, (*b*) Malignant lesions, carcinomas and sarcomas, (*c*) Rhinoscleromata, tubercle and syphilis, (*d*) midline eosinophilic granulomata of the nose, (*e*) other infections of the nose and paranasal sinuses which make up the rather bizarre group of undiagnosed tropical tumours of the nose and face.

Summary

An apparently previously undescribed lesion has been reported with details of its histology and points of difference from diseases of allied ætiology. The absence of a Mycologist has led to limitation of certain mycological details, but these in view of their unique histopathology may prove to be of academic interest only. The disease which was originally thought to be restricted to the limbs and trunks of certain nationalities has been shown not only to occur in other ethnological groups but also to have clinical variations in other parts of the body probably through another species or genus of the organism. Discovery of other manifestations in other nationalities must lead to second thoughts on the climatic and racial predilections of this large class of fungi, while the rapid increase in the variety and use of antibiotics, steroids and substitution therapy might even influence the clinical features and prognosis of its infections.

I am very grateful to Dr. Brew of the Department of Pathology for his help in preparing the slides for this paper and providing the description of the histology. I would also like to thank all the staff of the other ancillary services especially the medical illustration unit for their help.

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