ASPERGILLOMA

OF

THE PARANASAL SINUSES

by

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LETTER OF ASSIGNATION

The work on this thesis was done while I was seconded to the Department of Surgery, the University of Khartoum, as Senior Lecturer, for a period of two years 1964-1966. I was also Consultant Surgeon to the Khartoum Civil Hospital and the Sudan Military Hospital.

Owing to lack of local technical assistance it was necessary, but extremely difficult and inconvenient, to send specimens to Scotland for assistance in the completion of this work. The work in this thesis has been done by me, except where acknowledgement has been made in the following pages.

Chris. Thomasson

ACKNOWLEDGEMENTS

I wish to express my thanks to Dr. Branko Milosev who presented the problem which led to the work in this thesis and without whom the practical aspects would have been incomplete; to Dr. J. C. Gentles, Department of Mycology, Glasgow University, for his help and advice on the mycology; to Dr. A. T. Sandison, Department of Pathology, University of Glasgow, for not only the histology but also for his encouragement during the preparation of this thesis; to the Department of Photography, Bristol University for copying my photographs. I should also like to thank Dr. Habib Abdallah for the Xrays used and Miss M. J. Clare for her patience in typing my thesis.

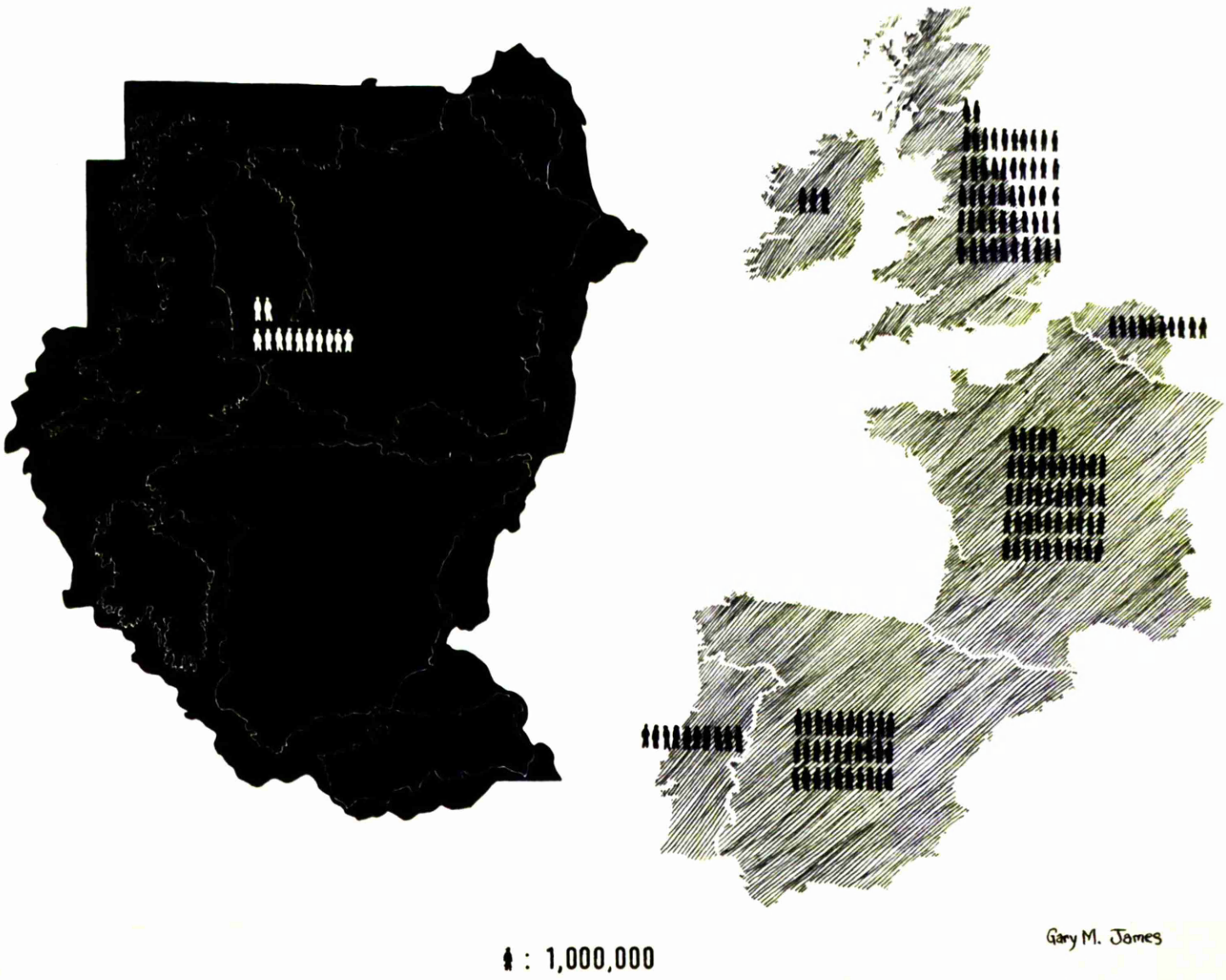


Fig. 1. A MAP OF THE SUDAN WITH INTERPOSITION OF THE BRITISH ISLES, BELGIUM, FRANCE, SPAIN AND PORTUGAL.

INTRODUCTION

Of the many countries which comprise the "Dark Continent" few possess a greater wealth of pathological material and a greater challenge to the medical research worker than the Sudan. It comprises an immense territory of over one million square miles (See Fig. 1) extending from Egypt in the North through the vast desert wastes of the Northern Sudan (See Fig. 2) down through the tropical swamps in the South (See Fig. 3) to Uganda, Kenya and the Congo. To the East are the Red Sea and Ethiopia, while to the West are Chad and the Central African Republic.

Prior to the nineteenth century the Sudan was very largely an unknown country, visited by only a few intrepid explorers. In 1820 the Northern and Western parts began to be opened up and a few trading posts were established in the South; progress, however, was suddenly arrested in 1881 by the rise of the Mahdi and the consequent rebellion plunged the country into chaos. Many years passed before the Sudan was reoccupied and a new era begun. In 1956 with the end of the Condominium the Sudan gained her Independence and at that time one of

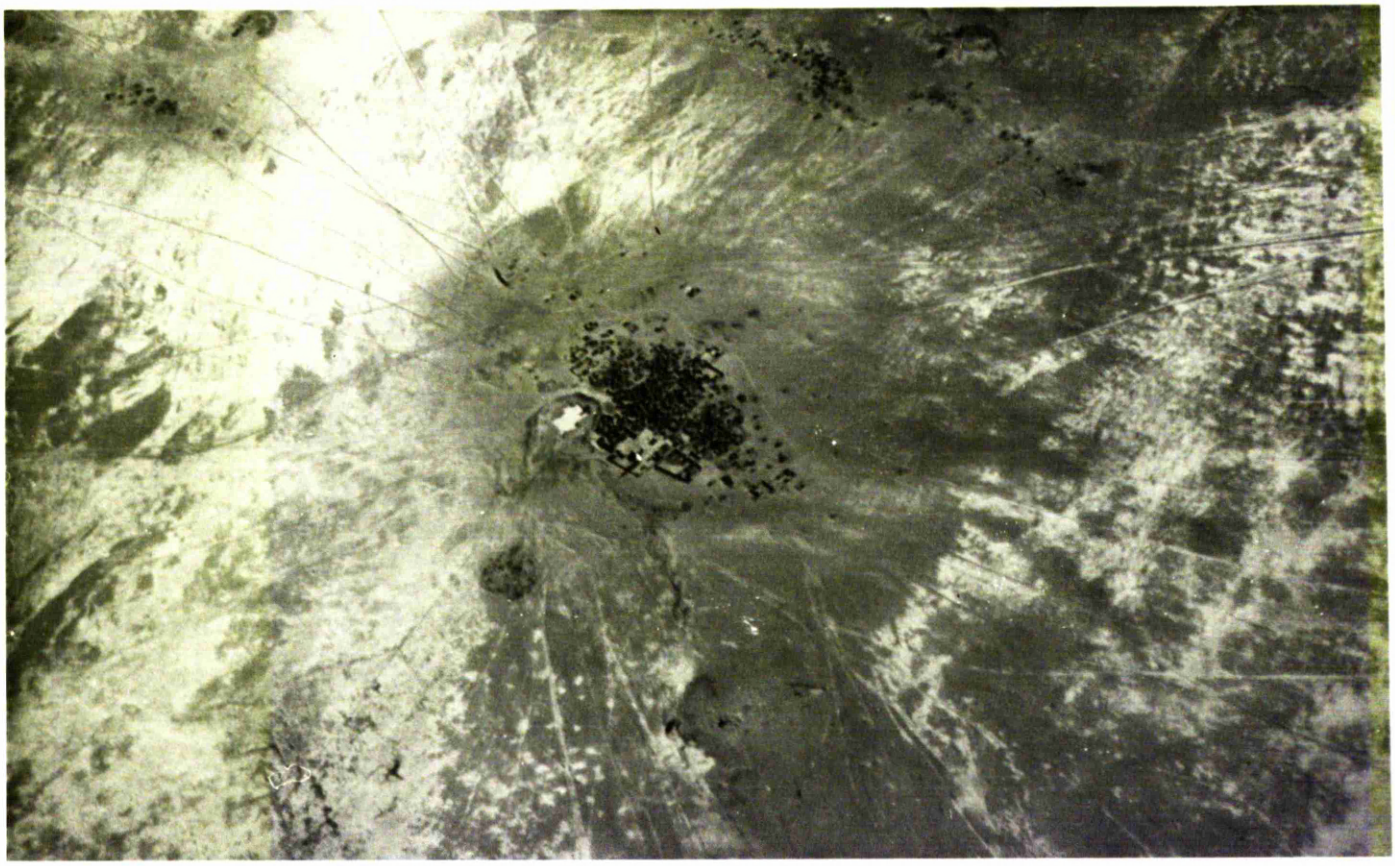


Fig. 2. A VILLAGE IN THE DESERT SHOWING RADIATING TRACKS FROM THE WATER HOLE.

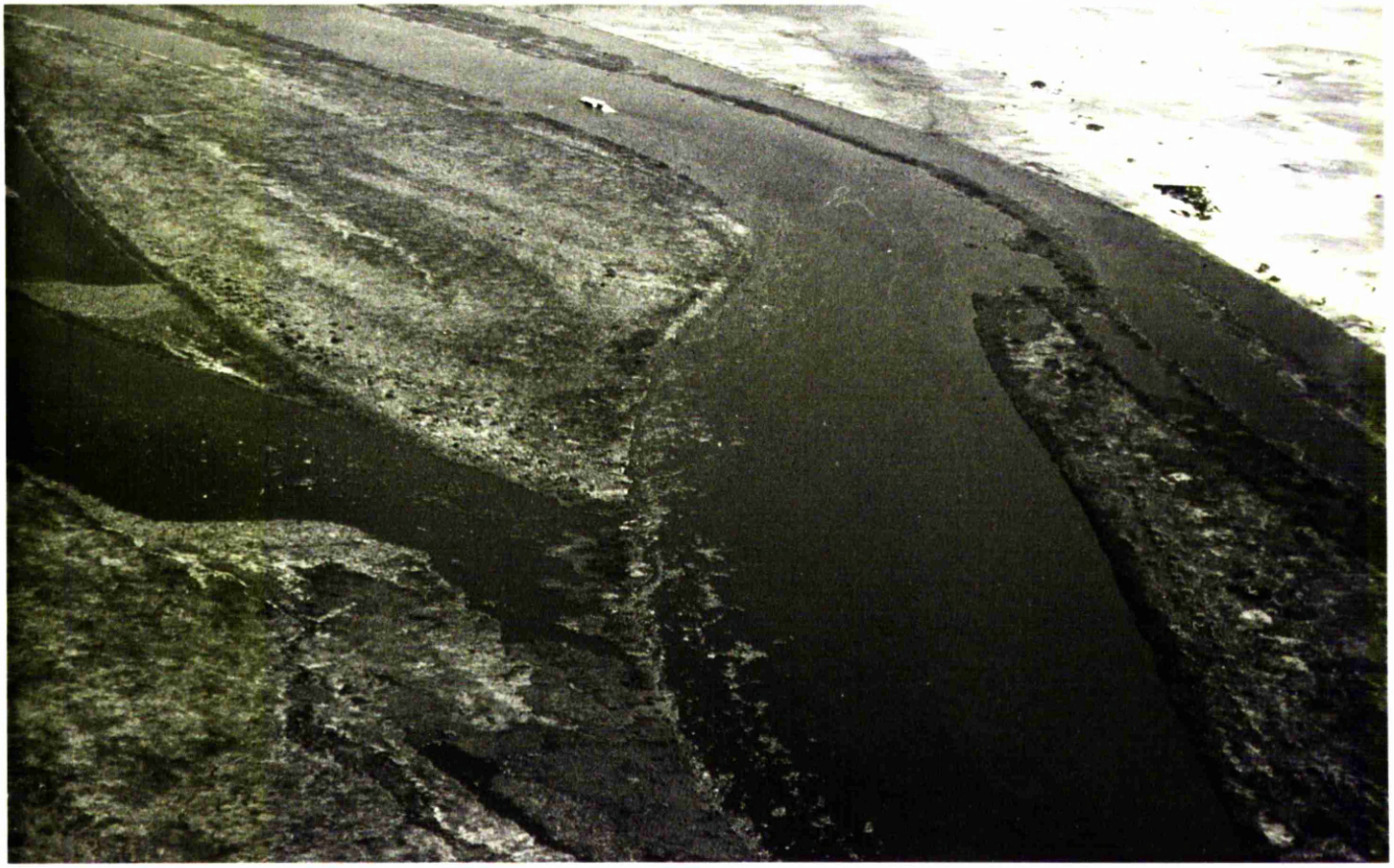


Fig. 3. THE SWAMPS IN THE SOUTHERN SUDAN.

the greatest medical services - The Sudan Medical Service which had pioneered medicine in all its forms throughout the Sudan, came to an end. From the time of her Independence until today the Sudan has faced all the problems of an emergent developing country and as a result of political revolutions, internal troubles and lack of funds, some regression, especially in medical care as a national concern has taken place.

The Sudan is probably the only country in the world where one encounters such a sharp distinction between those people living in the North and those in the South. The North is inhabited by Arabs who have gradually infiltrated southwards from Egypt and their way of life, customs and religion have nothing in common with those of Negro Nilotic stock in the South. Not only are the people different but the country and climate in which they live in no way match each other. As the people are relatively static in their habits the geographical distribution of disease, exemplified by Burkitt (1966), may readily be studied in the Sudan.

At the present time, with an approximate total population of eleven million, it is probably one of the most under-populated countries in the world with an average of four persons per square kilometre as compared with an average world population density of over twenty persons per square kilometre (Philosophical Society of Sudan 1958). (See Fig. 1) In spite of great advances in education, there is said to be only five per cent literacy throughout the country, although such figures may be misleading without a precise definition of literacy. As a large proportion of the Sudanese are dependent on animals for their livelihood, seasonal nomadic migration in search of water is mandatory and probably involves some forty per cent of the total population. (See Figs. 4 & 5). The last observation on general terms I should like to make concerns the present state of modern medical care; in the Sudan today probably a higher proportion of patients are treated by indigenous native medicine.

Fig. 4. CAMEL TRAIN ON THE MOVE.

Fig. 5. A NOMADIC CAMP IN THE DESERT.

With this brief account of the background of the country in which the work for this thesis was carried out, it is important, I believe, to be not only critical of the patients' symptomatology (amongst them daily suffering, foreign to the Western observer, is accepted) but also of the true incidence of disease in a country where a large number of the people are still suspicious of modern medical practice.

Speculation in the incidence of the clinical syndrome presented in this thesis (which up until now can be considered rare from the world literature), must be in the full knowledge that the established frequency of any condition is all too often related to the awareness of the observer.

Soon after my arrival in Khartoum (See Fig. 6) Dr. Branko Milosev, Consulting Ear, Nose and Throat Surgeon at the Khartoum Civil Hospital, presented me with one of his diagnostic problems:- A Northern Sudanese male with painless unilateral exophthalmos and a fixed hard mass at the inner canthus of his left eye.

Fig. 6. THE CITY OF KHARTOUM AT THE JUNCTION OF THE NILES.

Dr. Branko explained that this was not an uncommon problem for him and thereafter a planned investigation was started.

With some difficulty I arranged for specimens to be sent by air to the University Department of Pathology, The Western Infirmary, Glasgow, and there this tumour, which in many ways behaved like a locally malignant neoplasm, was found to be an aspergilloma. At a later stage the diagnosis was confirmed by culture of the operative specimen at the University Department of Medical Mycology, Glasgow.

Although I am only able to present a series of six patients it is the largest personal series of this condition on record. A limited, but relevant investigation on the environment of these patients with aspergilloma has been carried out and some possibilities as to the aetiology have been suggested. Following the good results of surgery in my cases, a form of treatment is recommended. Owing to lack of drugs alternative conservative measures could not be tried.

AN HISTORICAL REVIEW OF RELEVANT PAST WORK

In 1729 Micheli, a monk, was the first to describe spore heads and stalks and he called his findings ASPERGILLUS because of a resemblance to the brush used for sprinkling holy water - ASPERGILLUM (Raper and Fennell 1965). It was, however, more than one hundred years later that the Italian Agostino Bassi in 1835 gave the first experimental demonstration that one living organism may cause disease of another. He studied Muscardine in Silkworms (Ainsworth, 1952). Although interest had been aroused in the field of Mycology it was not until 1850 that Debarry produced reliable reports from his laboratory culture of moulds and thereafter a more accurate diagnosis became possible. Fresenius, Cramer, Wilhelm and Brefeld were developing the field of Mycology in Germany, while ten years later, in 1860, Raulin and Van Tieghan in France demonstrated the gallic acid fermentations from tannin in gall nut in their study of moulds. (Raper and Fennell 1965). The first publication, however, of the genus Aspergillus was made in 1901 in Hanover by Wehmer.

Aspergillus has long been a well recognised infective danger for birds in their early period of captivity in Zoological Gardens and was reported by De Reamur in 1813 in a Scaup duck (Ainsworth 1952). The first example in a mammal was probably a mycotic lung lesion in an Axis deer reported by Rousseau and Serrurier in 1841 (Raper and Fennell 1965). The earliest case of Aspergillus infection in man was that reported by Virchow in 1856.

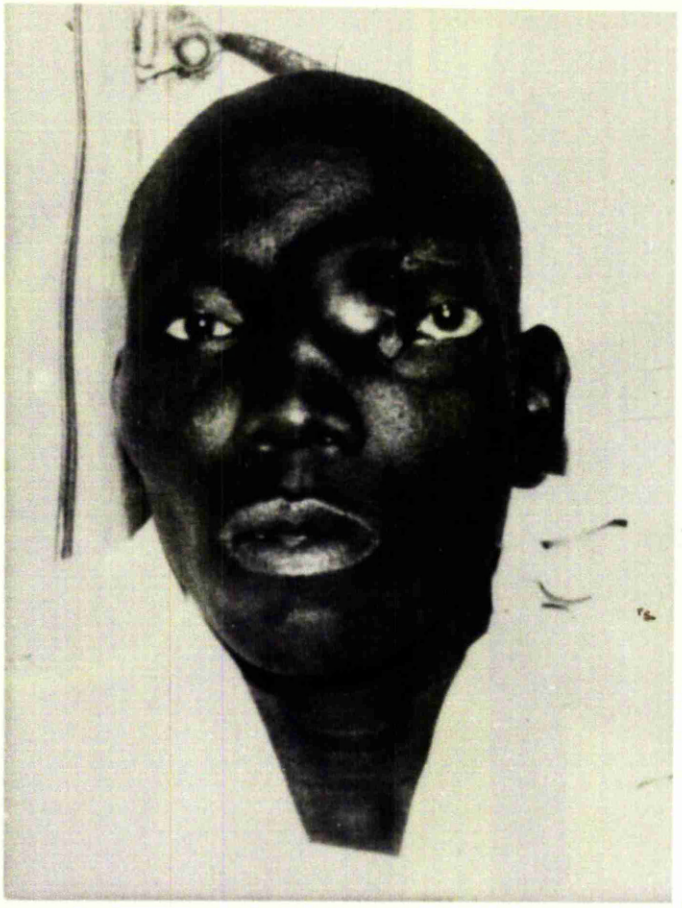
The first report of Aspergillus being isolated from the upper respiratory tract came from Berlin in 1891 when Zarniko described a case in a fifty year old woman, but it was not until 1927 that an Aspergillus granuloma was first described by Wright in a thirty-five year old man.

The first record of Aspergillus being found in the Sudan was a report by Archibald (1913) on the post-mortem findings in an Ostrich which he described as being typical of aspergilliosis (sic). Archibald in his paper suggested that aspergilliosis (sic.) was possibly responsible for a variety of human mycetoma occurring in the Sudan but like so many pioneers his observations were passed over and

filed along with many other original discoveries and suggestions.

MATERIALS AND METHODS

Six patients presenting the clinical picture of aspergilloma of the paranasal sinuses causing unilateral exophthalmos have been investigated. All the cases were male Northern Sudanese whose ages ranged from twenty to sixty years and their stated occupations were as diverse as student and farmer. They were studied clinically, radiologically, pathologically and in two instances mycologically.



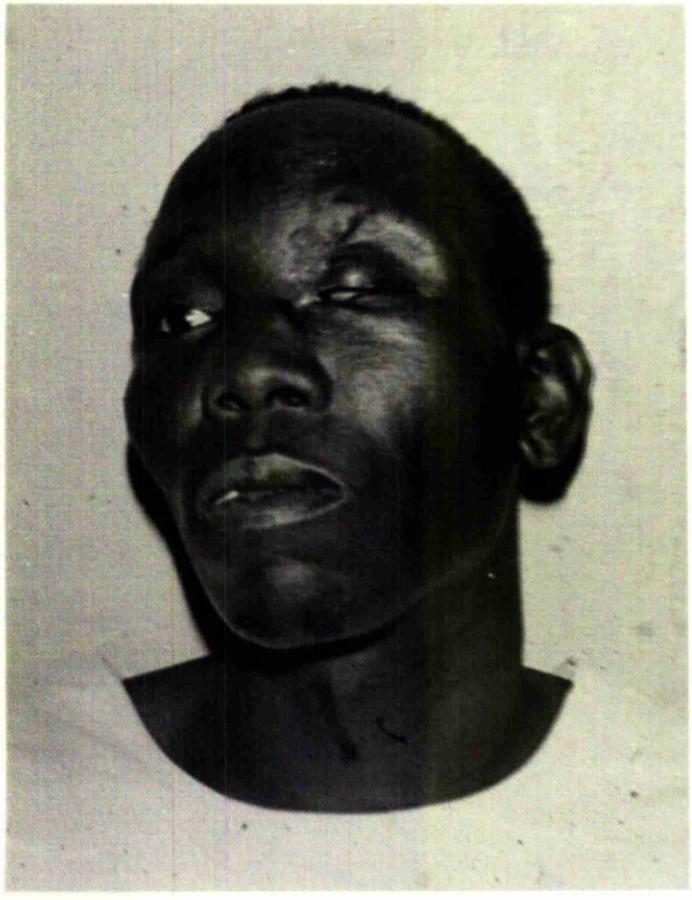


Fig. 7a. CASE NO. 1. Showing swelling at the left inner canthus.

Fig. 7b. Xray showing obliteration of the ethmoidal cells and thickening of the right antrum.

Fig. 7c. Postoperative - showing severe ptosis.

CASE REPORTS

Case No. 1 (See Fig. 7a)

A thirty year old male Northern Sudanese reported to hospital complaining of a painless swelling at the left inner canthus of ten years duration. He said that it had started as a small itchy nodule which slowly grew to its present size and that it had intermittently discharged purulent material. At the same time as the lump increased in size he noticed that his left eye was becoming more prominent. He gave no significant past history and it was clear that he had never been treated with antibiotics nor steroids.

On examination the significant findings were anterolateral proptosis of the left eye with no restriction of movement nor vision. There was a non-tender, firm to hard mass at the left inner canthus which was fixed to both the deep structures and the overlying skin. Endoscopy showed no abnormality of the ears, nose nor throat but

radiography showed thickening of the upper, medial and lower left orbital walls. The bones surrounding the left frontal sinus were not clearly outlined and the sinus was partially opaque. The ethmoidal cells were not visualised and the right maxillary sinus showed a thickened mucosa. (See Fig. 7b) Radiography of the chest revealed no abnormal features. Blood examination:- Haemoglobin 90%, W.B.C. 4,900/cmm., eosinophils 2%.

Under local anaesthesia the lesion was explored through a curved incision and a firm mass was discovered extending towards and involving the ethmoid sinuses. The roof of the ethmoid sinuses was eroded and the mass extended along the medial side of the optic nerve where the dura was found to be thickened. The mass was resected and the resulting cavity was packed with iodoform gauze and drained through the nose by a rubber tube. The pack and drain were removed on the fourth post-operative day and the patient made an uneventful recovery, being discharged

from hospital on the fourteenth day.

Histological examination of the resected material at the University Pathology Department of the Western Infirmary, Glasgow, showed an aspergilloma.

The patient was seen one year later and showed no evidence of recurrence nor residual proptosis. There was, however, moderate ptosis as a result of damage to the levator palpebrae superioris muscle. (See Fig. 7c).

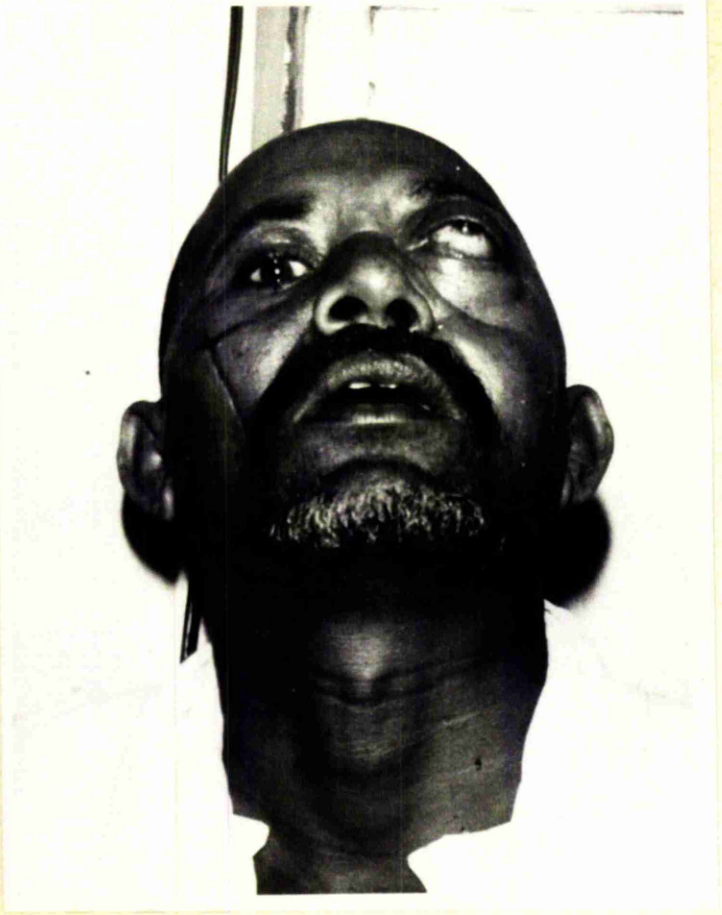


Fig. 8a. CASE NO. 2. Showing unilateral ocular proptosis.

Fig. 8b. Xray showing soft tissue mass filling the left maxillary sinus and orbit with severe bone destruction.

Fig. 8c. Postoperative picture showing wide communication between the orbit and nasopharynx.

Case No. 2

A sixty year old Northern Sudanese male reported to hospital complaining of swelling of his left cheek for one year and, more recently, prominence of his left eye. He stated that eight days prior to noticing the swelling of his cheek he had had a moderately severe epistaxis. He did not admit to having any pain and gave no relevant past history. At no time previously had he taken antibiotics nor steroids and he had enjoyed good health.

The patient was a fit-looking man who showed moderate proptosis of the left eye and prominence of the left maxilla. There was no limitation of eye movement nor of vision. Endoscopic examination showed only minimal bulging of the left lateral wall of the nose but radiography showed a large soft tissue mass filling the left maxillary sinus and extending into the orbit. The lateral walls of the orbit and maxillary sinus including the zygomatic bone were destroyed and there was thickening of the medial

wall of the sinus. Radiography of the chest showed no abnormality. Blood examination:- Haemoglobin 80%, W.B.C. 6,200/cmm., eosinophils 6%.

Under local anaesthesia, exploration revealed a firm fixed mass in the maxillary sinus extending into the orbit. A large biopsy was taken and reported locally in Khartoum as non-specific granuloma.

The patient was discharged but returned to hospital four years later because of progression of his symptoms. General examination showed no change in his physical state but he now had severe proptosis of his left eye, restriction of all movements of that eye, corneal opacities and partial blindness. (See Fig. 8a).

Under general anaesthesia, exploration on this occasion demonstrated a very large firm mass filling the left maxillary sinus, causing severe local bone destruction and extending into the left orbit and up to the base of the skull. (See Fig. 8b)

Exenteration of the orbit and partial removal of the remaining tumour mass was carried out. During these manipulations in an endeavour to remove the adherent mass the dura was opened with some loss of cerebro-spinal fluid. The medial wall of the maxillary sinus was completely removed to allow free communication with the nose and nasopharynx. The cavity was packed with iodoform gauze for four days and following an uneventful post-operative recovery the patient was discharged home thirty days after the operation. Eight months later, when the large cavity was found to be lined with healthy mucosa, closure by rotation skin flaps was carried out. (See Fig. 8c)

Biopsy material from the second operation was reported at the University Pathology Department of the Western Infirmary, Glasgow, as aspergilloma.

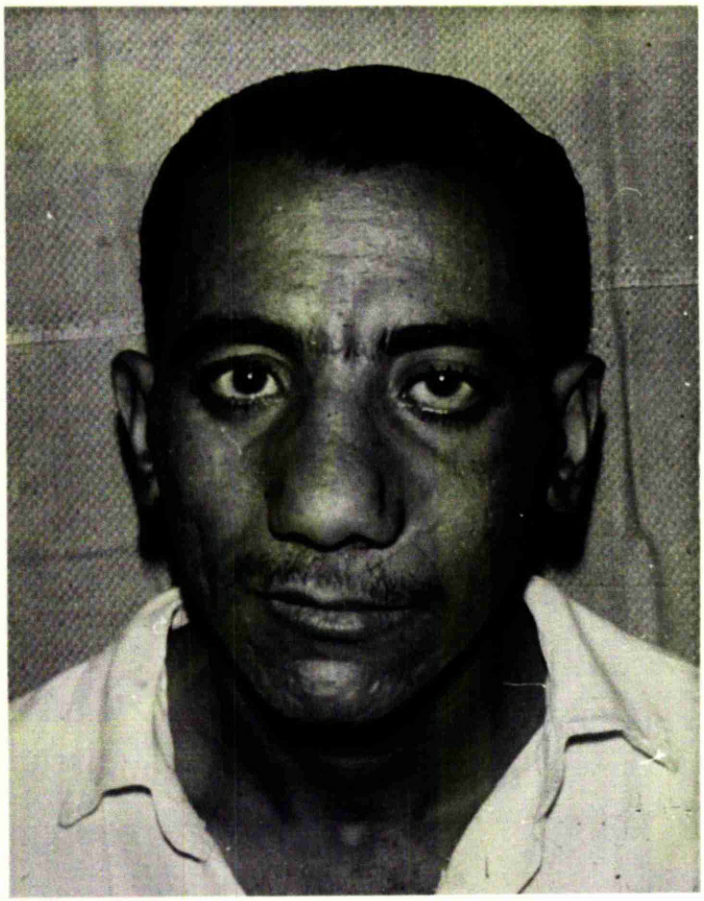


Fig. 9a. CASE NO. 3. Showing prominence of the left cheek.

Fig. 9b. Xray showing destruction of the left antral walls.

Case No. 3

A twenty year old Northern Sudanese male student reported to hospital with a complaint of slowly progressive nasal obstruction, rhinorrhoea and frontal headache of five years duration. Nasal polypectomy and a bilateral Caldwell-Luc operation were performed in 1961 but six months later left nasal obstruction recurred and a further polypectomy and Caldwell-Luc operation were performed in 1962. Two years later in 1964 he had a further exploration performed and biopsy removed at this operation was reported locally in Khartoum as non-specific granuloma.

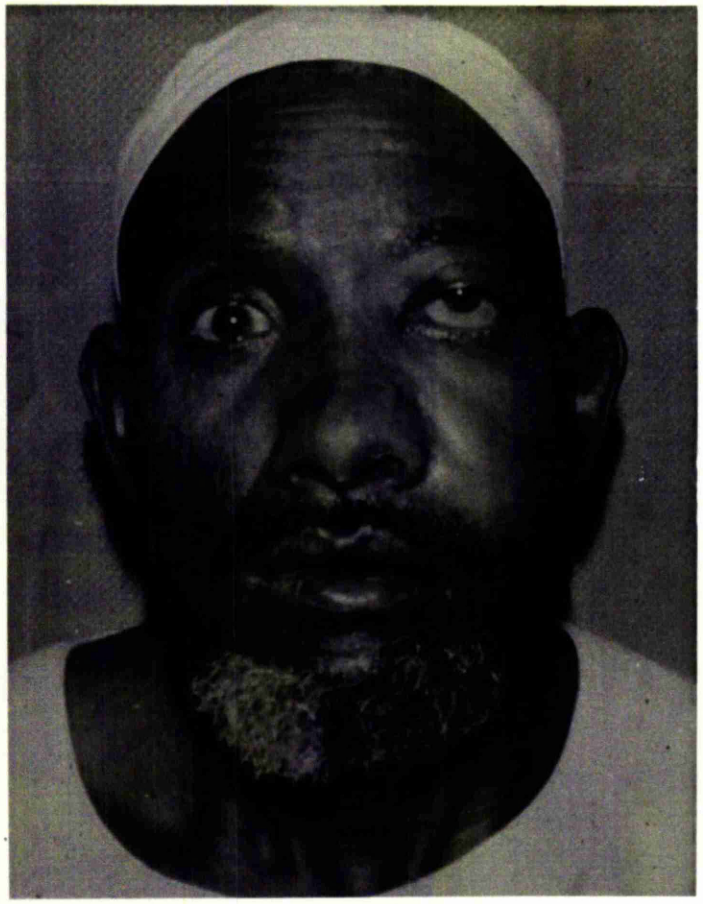
One year later, that is to say in 1965, he returned to hospital complaining of swelling of his left cheek. (See Fig. 9a). At this time examination showed no abnormality other than a non-tender, hard prominence of the left maxilla. There was mild proptosis of the left eye but no limitation of eye movement nor of vision. There was no cervical lymphadenopathy. Rhinoscopy showed left sided nasal

obstruction due to medial displacement of the lateral wall of the nose and prominence of the left lateral wall of the nasopharynx and hard palate on the same side. Radiography showed considerable bone destruction of the left antral walls and destruction of the medial wall of the right antrum. Both sinuses were partially opaque. (See Fig. 9b). Radiography of the chest revealed no abnormality. Blood examination:- Haemoglobin 80%.

Under general anaesthesia exploration was carried out through an extended Caldwell-Luc approach. This approach showed a large, fixed, hard mass infiltrating all walls of the sinus with destruction of the orbital floor and also extension into the nasopharynx. The mass was removed and free drainage obtained to the nose by removal of the medial wall of the sinus. The cavity was packed with iodoform gauze for four days and after an uneventful post-operative recovery the patient was discharged home on the fourteenth day.

Histological examination of the surgical specimen at the University Pathology Department of the Western Infirmary, Glasgow, showed the lesion to be an aspergilloma.

Six months after surgery there was no local evidence of disease and a small oro-antral fistula was closed. One year after operation the patient's only complaint was of slight infra-orbital neuralgia.



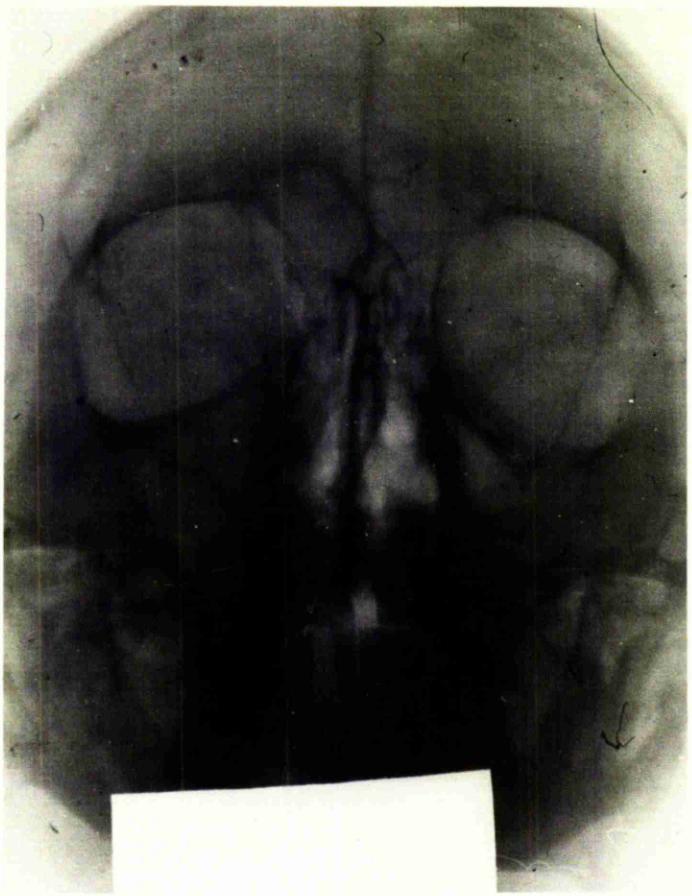


Fig. 10a. CASE NO. 4. Showing left ocular proptosis and ptosis along with prominence of the left cheek.

Fig. 10b. Xray showing orbital asymmetry and depression of the left orbital floor. The lower ethmoidal cells are opaque. The left antral wall is destroyed and both antra are opaque.

Fig. 10c. Showing left sided enophthalmos.

Case No. 4. (See Fig. 10a)

A forty year old Northern Sudanese male was referred from the Eye Hospital to Khartoum Civil Hospital with a four year history of left sided frontal headache and progressive left sided proptosis of one year's duration. He gave no relevant past history and did not admit to any nasal discharge. At no time had he taken antibiotics nor steroids.

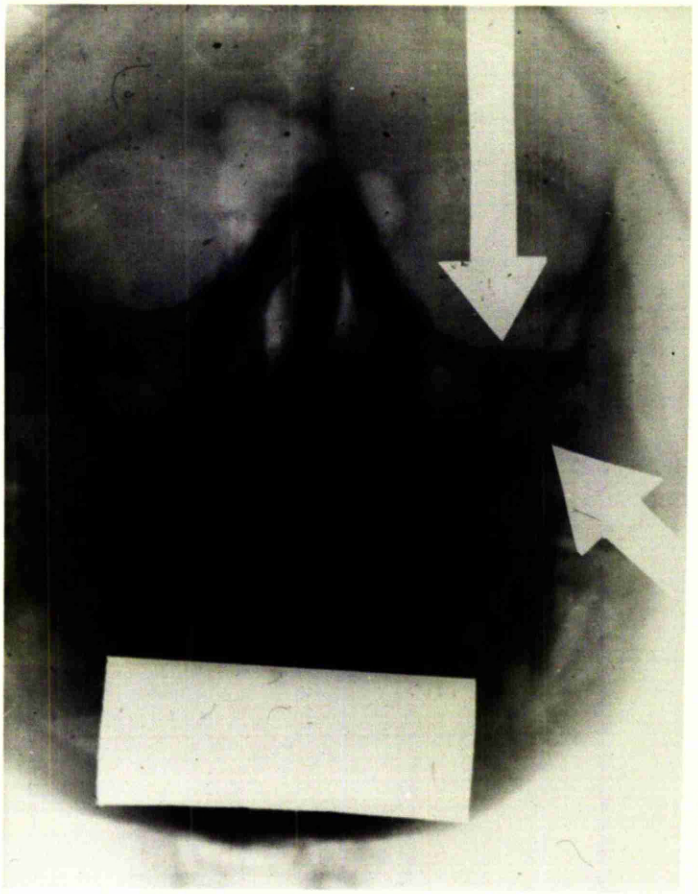
Examination showed a firm non-tender mass in the floor of the left orbit causing unilateral proptosis and ptosis. Prominence of the left maxilla was also evident. Endoscopy showed no abnormality of the ear, nose nor throat but radiography showed orbital asymmetry and the floor of the left orbit was depressed. The lower ethmoidal cells were partially opaque; there was reduced translucency of both maxillary sinuses. (See Fig. 10b). Radiography of the chest revealed no abnormality. Blood examination:- Haemoglobin 80%, W.B.C. 5,800/cmm., eosinophils 2%.

Under general anaesthesia exploration of the left

maxillary sinus was carried out through a Caldwell-Luc incision. A large firm, fixed mass was found which infiltrated through the orbital floor, backwards to the pterygo-palatine fossa and upwards to the base of the skull. The mass showed some central necrosis but was suitable for resection. Free drainage of the resulting cavity was obtained by complete removal of the medial wall and part of the posterior wall of the maxillary sinus. An iodoform pack was left in the cavity for four days and thereafter the patient made an uneventful post-operative recovery, being fit for discharge on the fourteenth post-operative day.

Histological examination at the University Pathology Department of the Western Infirmary, Glasgow showed the lesion to be an aspergilloma.

When seen at follow-up one year later no evidence of residual disease could be found but there was some left enophthalmos with limitation of both lateral and upward movement of the eye. It was also noted that the globe on the left side was lower than on the right. (See Fig. 10c).



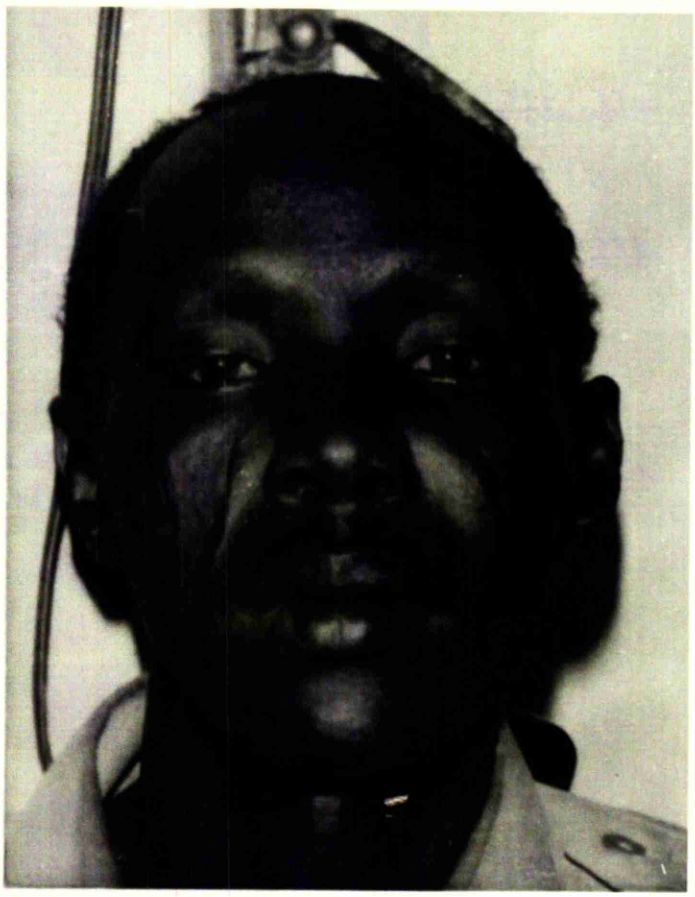


Fig. 11a. CASE NO. 5. Showing prominence of the left cheek.

Fig. 11b. Xray showing bone change in the floor of the left orbit and destruction of the left lateral antral wall.

Fig. 11c. Postoperative.

Case No. 5. (See Fig. 11a)

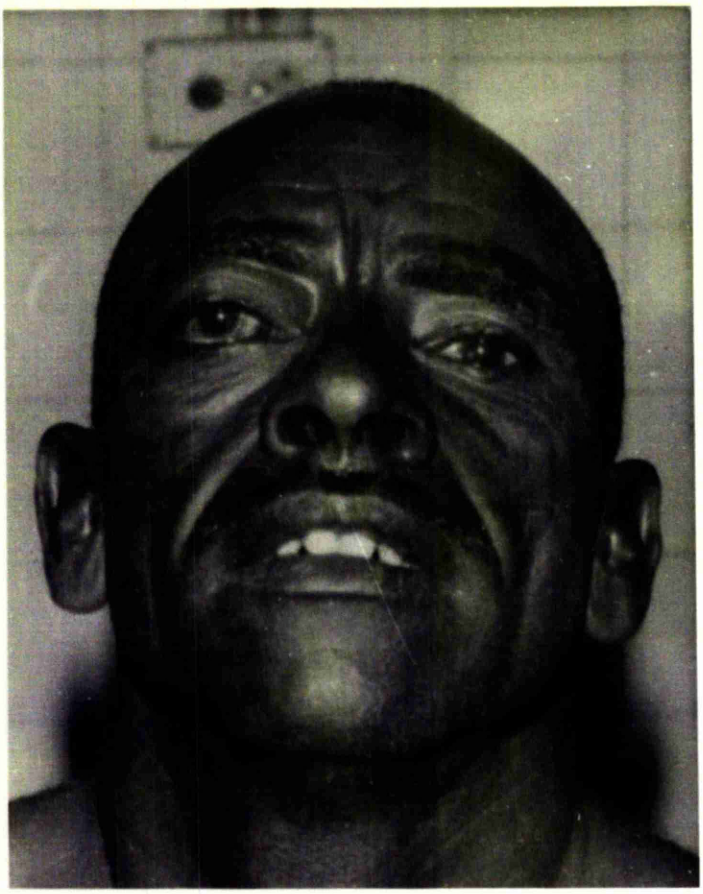
A thirty year old Northern Sudanese male reported to hospital complaining of a painless swelling of his left cheek during a period of two years. He claimed that it had started as a small nodule which gradually and progressively increased in size. He gave no relevant past history; he had always enjoyed good health and at no time had he taken antibiotics nor steroids.

On examination the only abnormality was a hard fixed non-tender mass intimately adherent both to the skin and deeper structures in the region of the left maxilla. Endoscopic examination showed no abnormality of the ears, nose and throat but radiography showed lack of structural detail of the left orbital floor and bone destruction of the lateral wall of the antrum. (See Fig. 11b).

Radiography of the chest and haematological examination showed no abnormality and the Kahn test was negative.

Under general anaesthesia, using an extended Caldwell-Luc approach a large, firm, fixed mass was found which could only be removed from the skin by sharp dissection. The mass filled the maxillary sinus and had destroyed both the roof and posterior walls of the antrum extending up to the base of the skull. The mass was completely removed and effective drainage into the nose established by removal of the medial wall of the sinus. An iodoform pack was left in the cavity for four days and when removed some bleeding occurred. The patient's post-operative recovery was uneventful, apart from some oedema of the left cheek and upper lip which did not delay his discharge from hospital on the fourteenth day. (See Fig. 11c).

Histological examination at the University Pathology Department of the Western Infirmary, Glasgow showed the lesion to be aspergilloma.



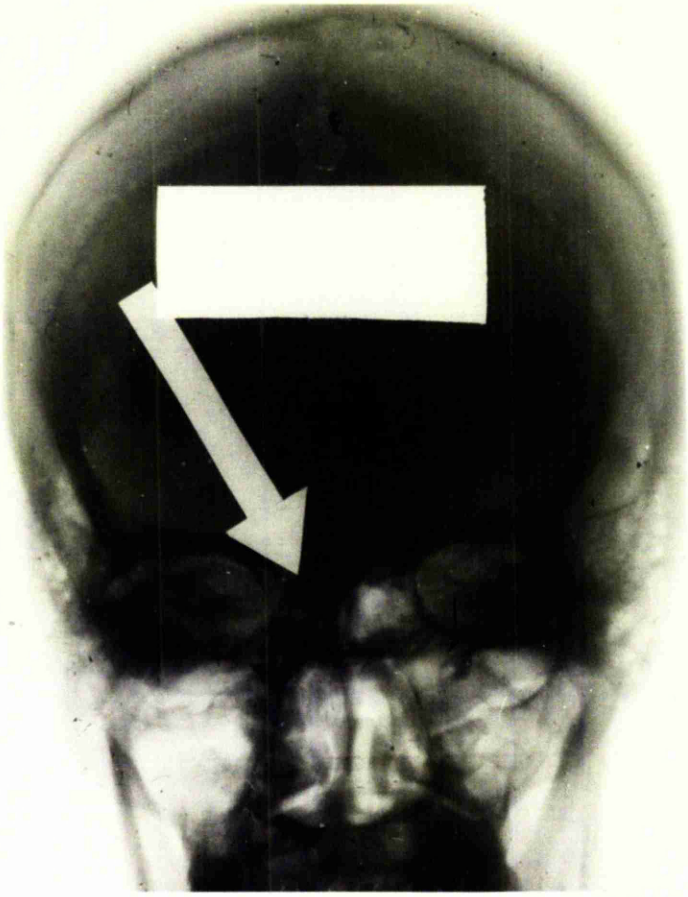


Fig. 12a. CASE NO. 6. Showing Right ocular proptosis.

Fig. 12b. Xray showing opacification of the Right ethmoid sinuses.

Fig. 12c. Postoperative.

Case No. 6. (See Fig. 12a)

A forty-five year old Northern Sudanese male reported to Hospital complaining of progressive bulging of his right eye during the previous two years. He admitted to no pain nor constitutional upset and he had always enjoyed good health. At no time had he taken any antibiotics or steroids.

Examination showed a non-tender prominence of the right maxilla and proptosis of the right eye without limitation of movement or vision. Endoscopic examination showed no abnormality of the ear, nose or throat but radiography showed that the medial portion of the orbital margin was not clearly outlined and in its lateral portion there was increased bone density. The ethmoidal cells were not clearly demonstrated and the right maxillary sinus showed reduced pneumatisation. (See Fig. 12b). Radiography of the chest was within normal limits. Sputum examination showed no pathogenic organisms and the Kahn test was negative.

Under general anaesthesia, using a modified

Caldwell-Luc approach a mass arising from the ethmoidal sinuses and extending through the orbit to the maxillary sinus was found. The mass was completely removed from both the ethmoid and maxillary sinuses but it could not be completely cleared from the orbit without sacrifice of the eye.

Complete drainage through the nose was obtained by removing the medial wall of the maxillary sinus. The cavity was packed for four days with iodoform gauze which caused some bleeding when it was removed. The post-operative recovery was satisfactory apart from some oedema of the right cheek and the patient was discharged on the sixteenth day. (See Fig. 12c)

Histological examination of the operative specimen at the University Pathology Department of the Western Infirmary, Glasgow showed the lesion to be an aspergilloma.

PATHOLOGY

All the specimens were tough, fibrous and greyish-white when received in 10% formol saline at the Western Infirmary, Glasgow, but cut easily with a knife.

Routine sections stained by the haemalum and eosin method showed a background of fibrous tissue. In places this was not particularly cellular but in others there were abundant infiltrates comprising plasma cells, lymphocytes, neutrophil and eosinophil polymorphs and active fibroblasts. (See Fig. 13 & 14).

The most striking feature was the presence of numerous and conspicuous giant-cells of Langhans type. Their numbers varied from place to place but sometimes amounted to about ten per high power field. They varied in size and shape as well as in the number and position of the nuclei; it is probable, however, that this variability largely reflects differences in the plane of section of the cells by the microtome knife. The giant-cells were usually characteristically oval or polyhedral with pink and somewhat hyaline cytoplasm but there was considerable variation in shape. The nuclei were vesicular and usually peripheral but sometimes forming central aggregates; they varied in number from five to fifty or more in each cell.

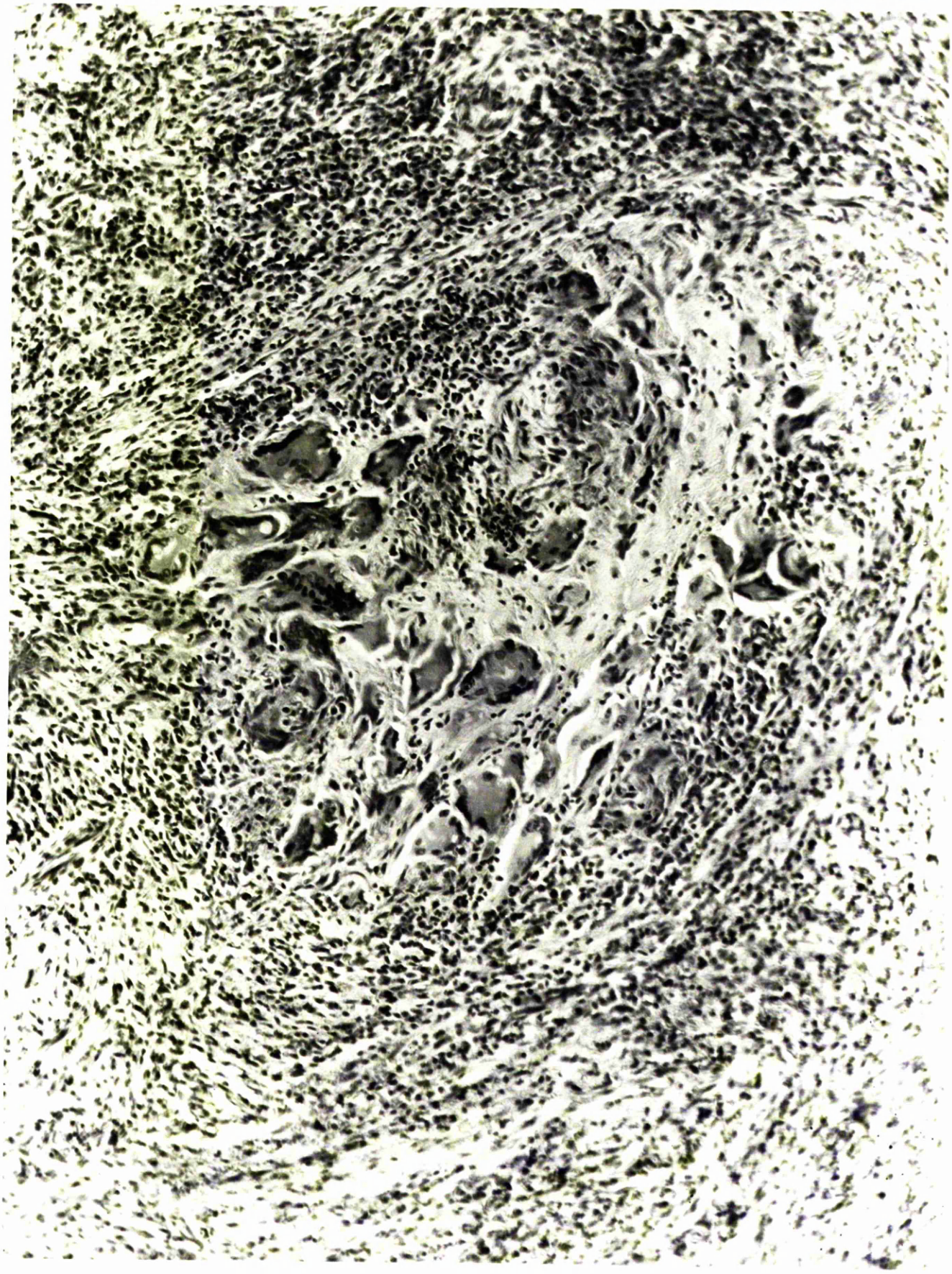


FIG. 13. Low power-view of orbital granuloma to show number and distribution of giant cells. Haemalum and Eosin x 300.

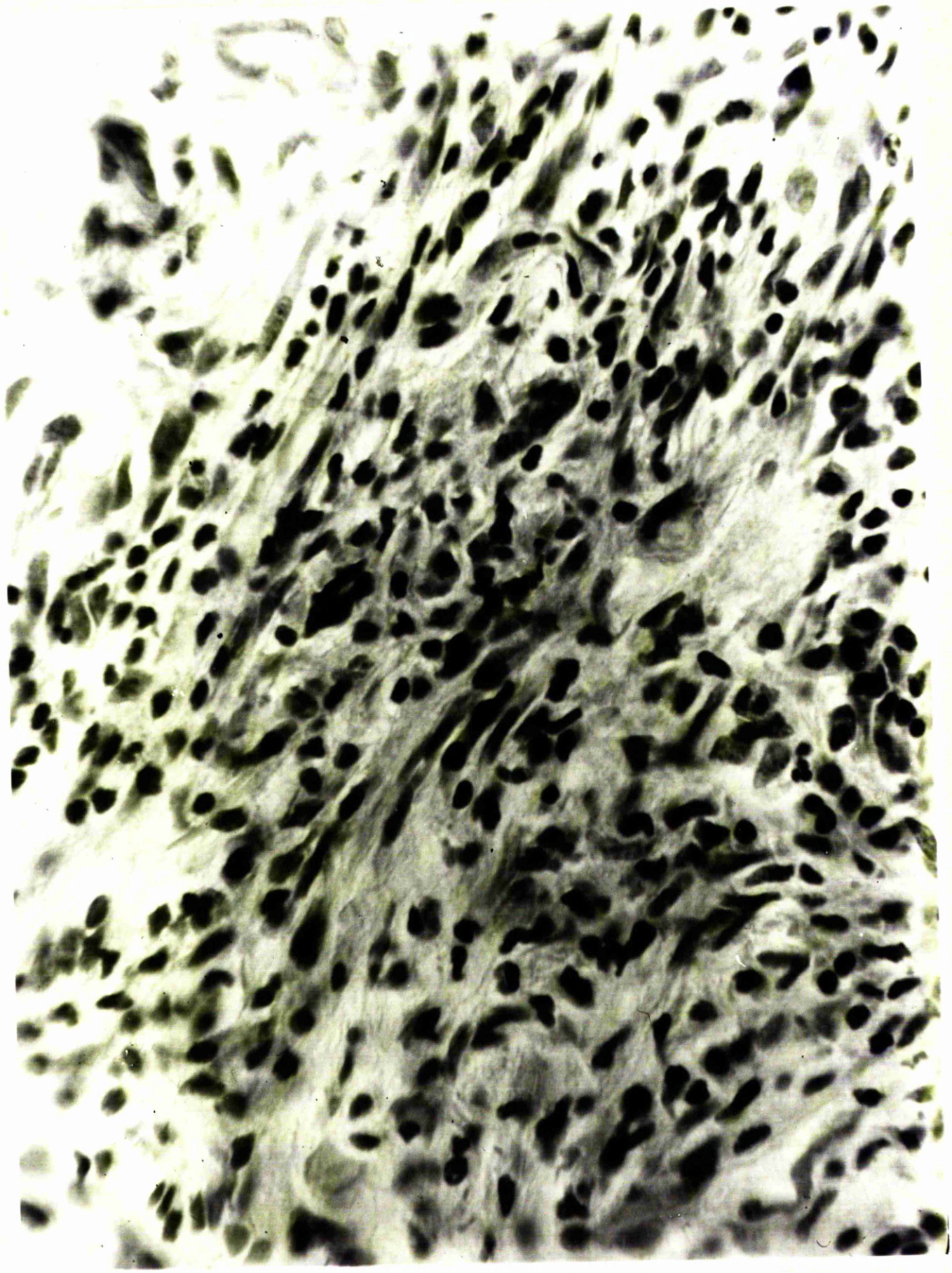


Fig. 14. High power view of granuloma to show non-specific infiltrate of lymphocytes, plasma cells and eosinophil polymorphs. H. and E. x 1350.

Some giant-cells were seen to contain clear vesicles which on careful examination could just be seen to contain slightly refractile bodies; the latter were circular or linear. (See Fig. 15 & 16) Very occasionally these bodies showed fugitive haematoxyphilia. Sometimes giant-cell systems were seen to be applying themselves to similar linear refractile bodies which were also present in the fibrous tissue. These bodies were believed to be possibly of fungus type. (See Fig. 17).

Accordingly, sections were stained by the periodic-acid/Schiff method and these showed the refractile structures to be indeed the septate hyphae of a fungus of appearance consistent with the diagnosis of an aspergillus. (See Fig. 18). This was further confirmed by application of the Gomori-Grocott silver methenamine method (Grocott 1955) which gave preparations in which photography of the hyphae was particularly effective. (See Fig. 19).

Published photographs similar to those shown in this thesis are scarce but there is an excellent example in the atlas of Hogan and Zimmerman (1962) which depicts an orbital aspergilloma. Moss and McQuown (1960) illustrate the giant-cell reaction to aspergillus in the tissue of the brain.

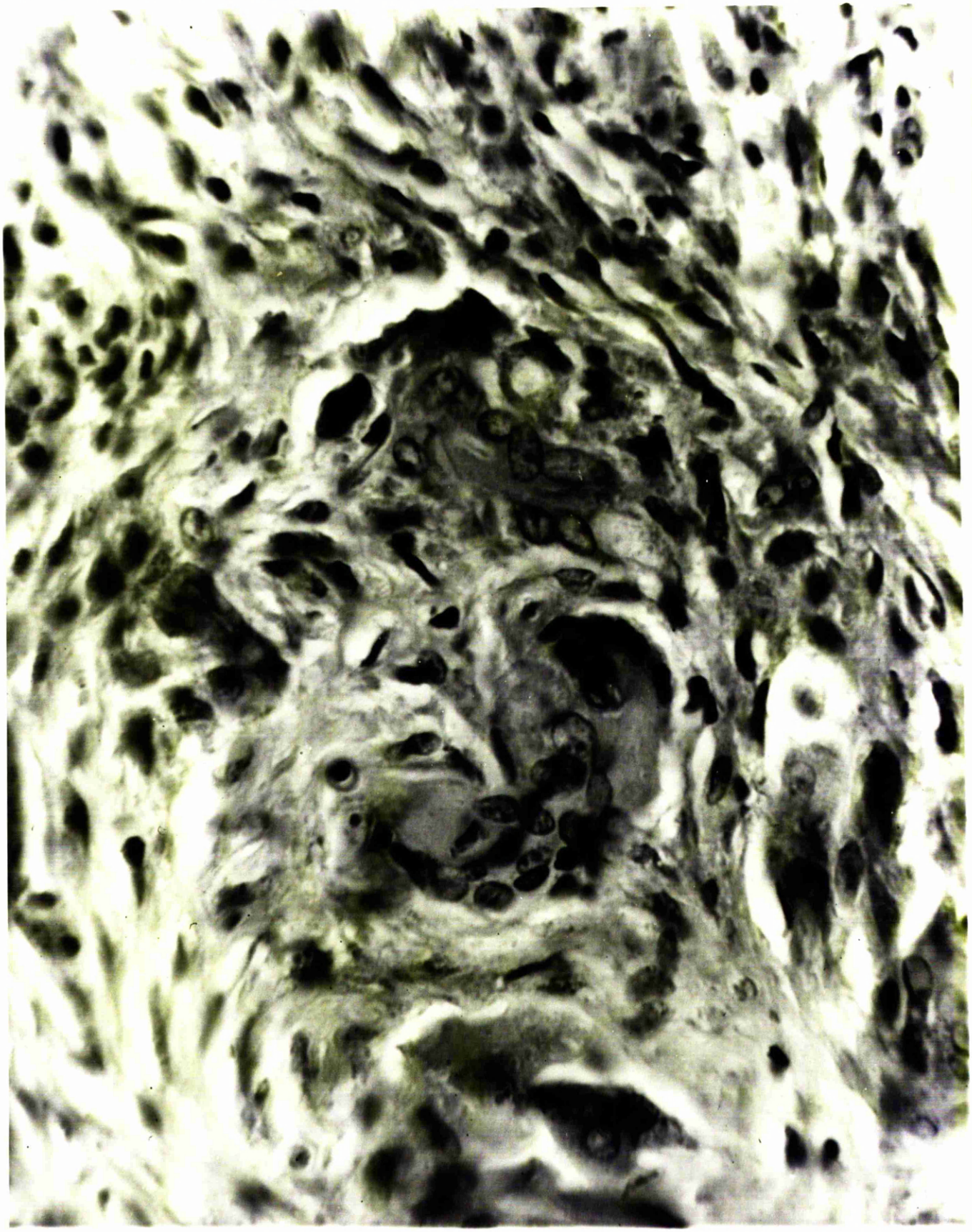


Fig. 15. High power view of giant-cells in which negatively-staining linear spaces are seen with difficulty. H. and E. x 1350.

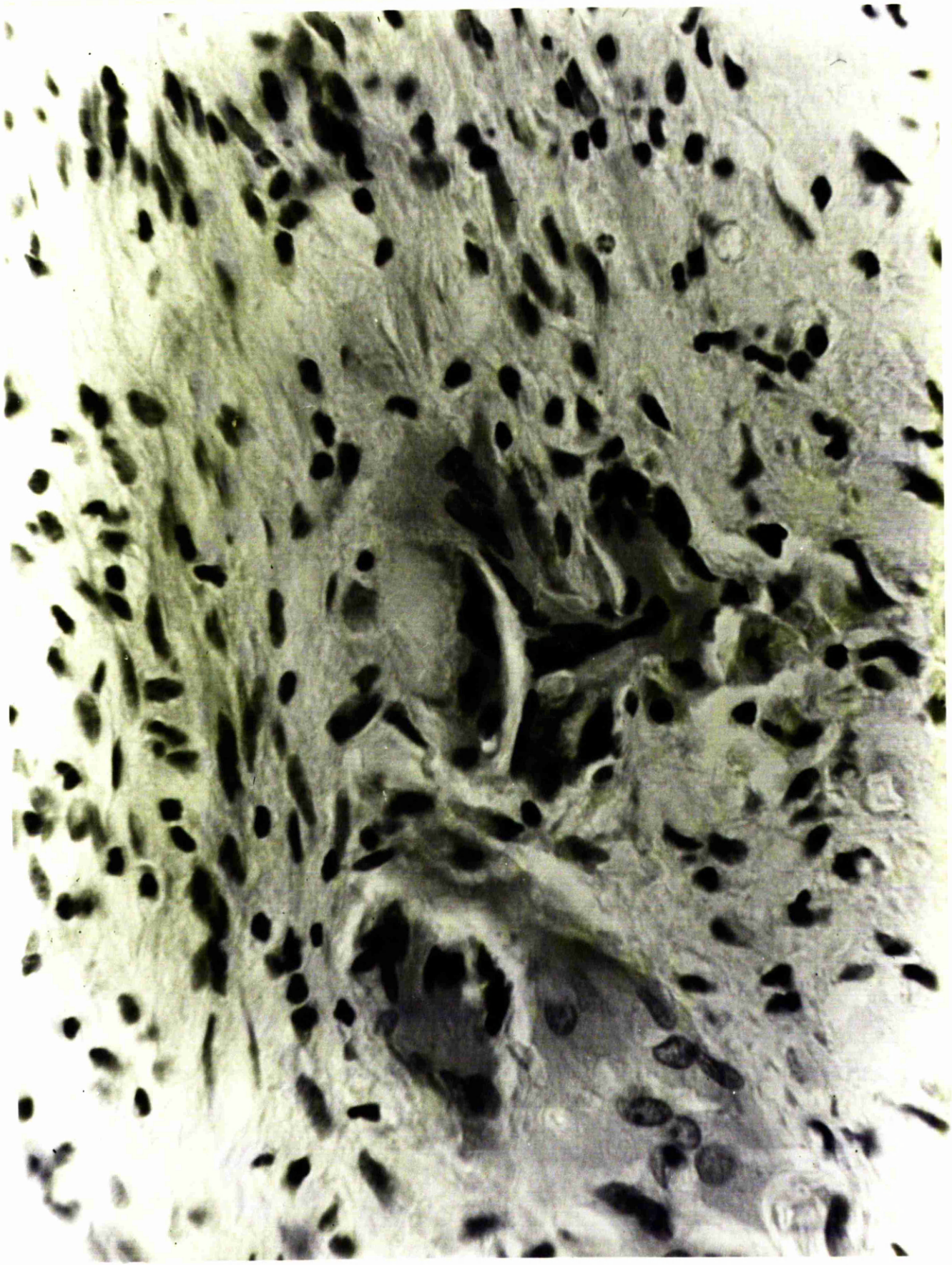


Fig. 16. High power view of giant-cell showing short, curved negatively-staining space. H. and E. x 1350.

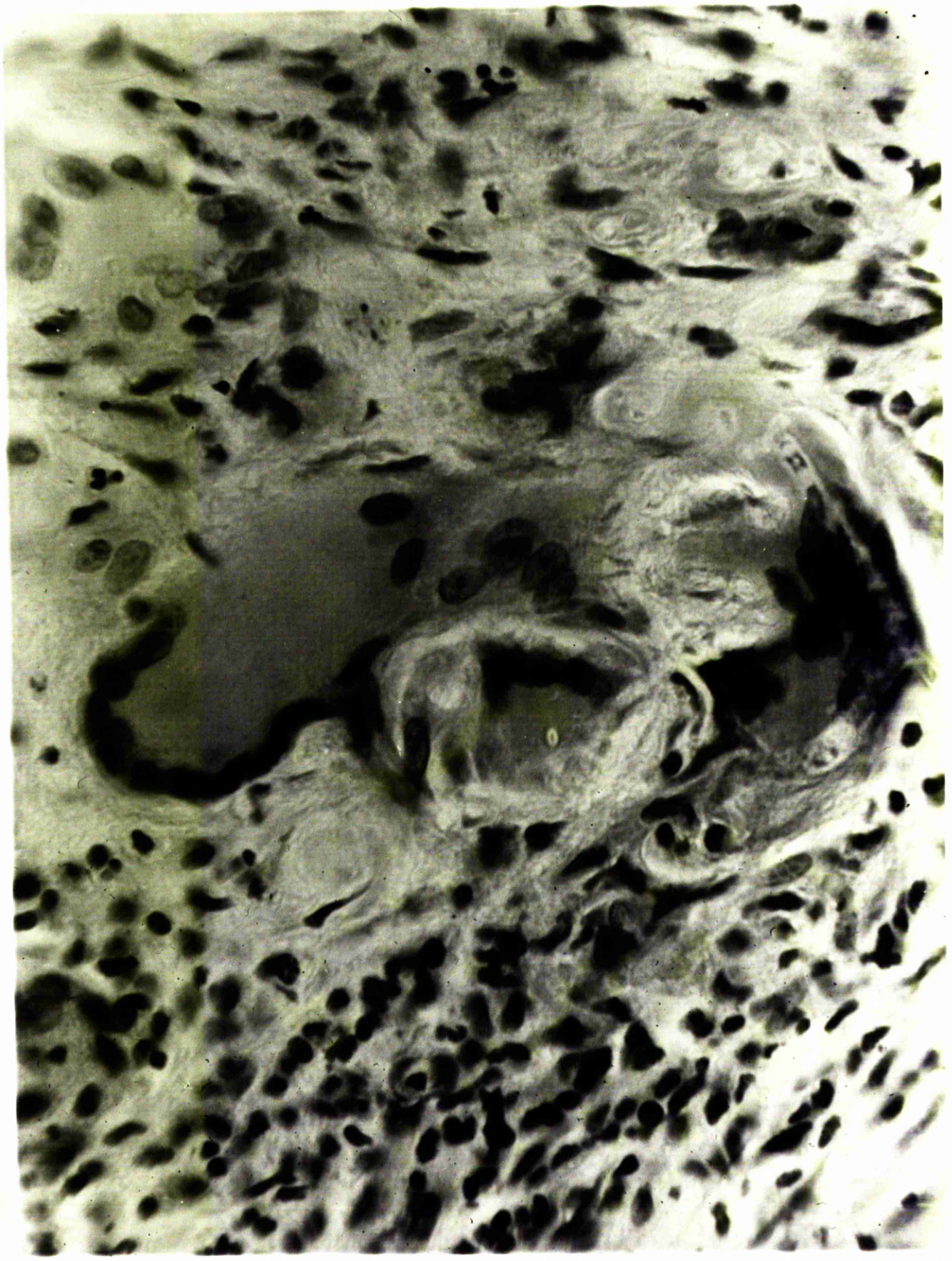


Fig. 17. High power view of giant-cell system showing complex arrangement of negatively-staining space in which septate pattern becomes apparent. H. and E. x 1350.

Fig. 18. High power view of giant-cell system in which septate hyphae are revealed by Periodic-acid Schiff staining x 1350.

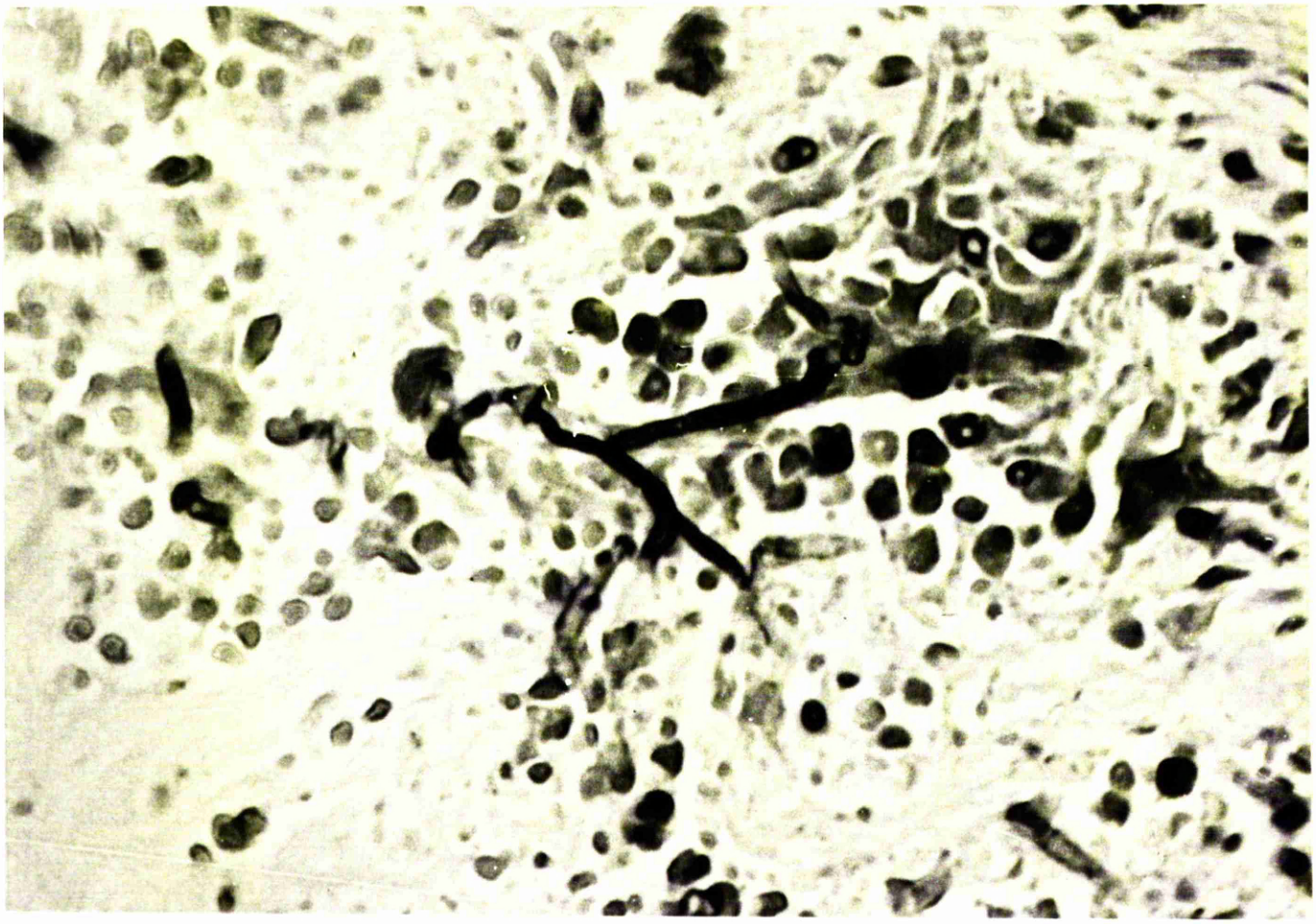


Fig. 19. High power view to show Hyphae Stained Deeply by Gomoris' Methenamine Silver Technique.

MYCOLOGY

Long before the advent of the microscope man was aware of the presence of moulds of different colours. It is true to say therefore that the existence of different fungi was appreciated hundreds of years before bacteria were discovered. Micheli, a monk, in 1729 was the first to recognise spore heads and stalks and thus pioneered the subject of mycology. As outlined in the Introduction, it was in 1835 that the Italian Agostino Bassi was the first to show experimentally that one living organism could cause disease in another by the example of muscardine in silk worms. Thereafter the relationship of living organisms to disease was soon recognised in man, but soon a total shift of emphasis was to take place through the work of Pasteur and Koch. Mycology was overshadowed by Bacteriology and later Virology and only now is slowly regaining significance in Pathology. It would be wrong at this stage to compare the importance of Mycology with Bacteriology and Virology but with the recent discovery of aflatoxin in aspergillus the importance of the fungi will require

further evaluation.

Fungal infections in humans were first reported by Virchow (1856) and it is generally recognised that such infections are acquired from man's environment unlike bacterial and viral infections which usually pass from person to person or animal to person.

Henrici (1940) divided mycotic lesions into superficial and deep, and stressed the point that the superficial group were self-limiting and rarely fatal while deep-seated infection was progressive and often fatal. Von Pirquet suggested that a parasite was not injurious directly but only after the cells of the host became sensitised to its products; Pfeiffer on the other hand suggested that the protoplasm of the invading organism contains endotoxins which are released on death and disintegration of the parasite. (Ainsworth 1952).

The Aspergillus group are widely distributed in nature and can readily be isolated from soils particularly those from tropical and subtropical areas. These fungi are derived from forage and decaying vegetation, stored seeds,

grains and various types of food products. Some aspergilli are known to be pathogenic to insects and less commonly to higher animals including man. It is true to say that this group of fungi have been more widely used commercially than any other group of moulds.

Aspergilli have been a well recognised hazard to birds in their early period of captivity in Zoological Gardens and it is interesting to note that the earliest reports by De Reamur (1813), Mayer and Emmert (1815) and Rayer and Montague (1842) isolated the fungus in the air sac of a Scaup duck, a jay and a bullfinch respectively, a situation where one could imagine only slight movement of air.

The first report I can find of Aspergillus in the Sudan is that of Archibald (1913) who reported death of an Ostrich due to Aspergilliosis (sic). He remarked at that time that there was reason to believe that aspergilliosis (sic.) was responsible for a variety of human mycetoma found in the Sudan, but as far as I can find this suggestion with regard to human disease passed unnoticed.

It is not surprising, in view of the very large number of spores, which are formed and which are easily dispersed in the air, that aspergilli are most frequently encountered as respiratory pathogens (Austwick 1965).

Many of the 18 species groups of aspergilli have been implicated in production of disease but the most frequently implicated is A. fumigatus. However, according to Austwick (1965), since A. flavus has been obtained from many lesions in man and animals, this species may be under certain conditions of equal significance to A. fumigatus as a cause of disease. It would seem probable that a predominance of one or other of these species is the factor which decides the species to be implicated as the causal agent of the disease.

From the limited, but relevant, investigations which have been made in the environment of these aspergilloma cases A. flavus predominated over all Aspergilli and A. fumigatus was not found. (See Fig. 20 & 21). A similar finding from much more extensive investigations has been reported from Israel (Abraham et al 1966).

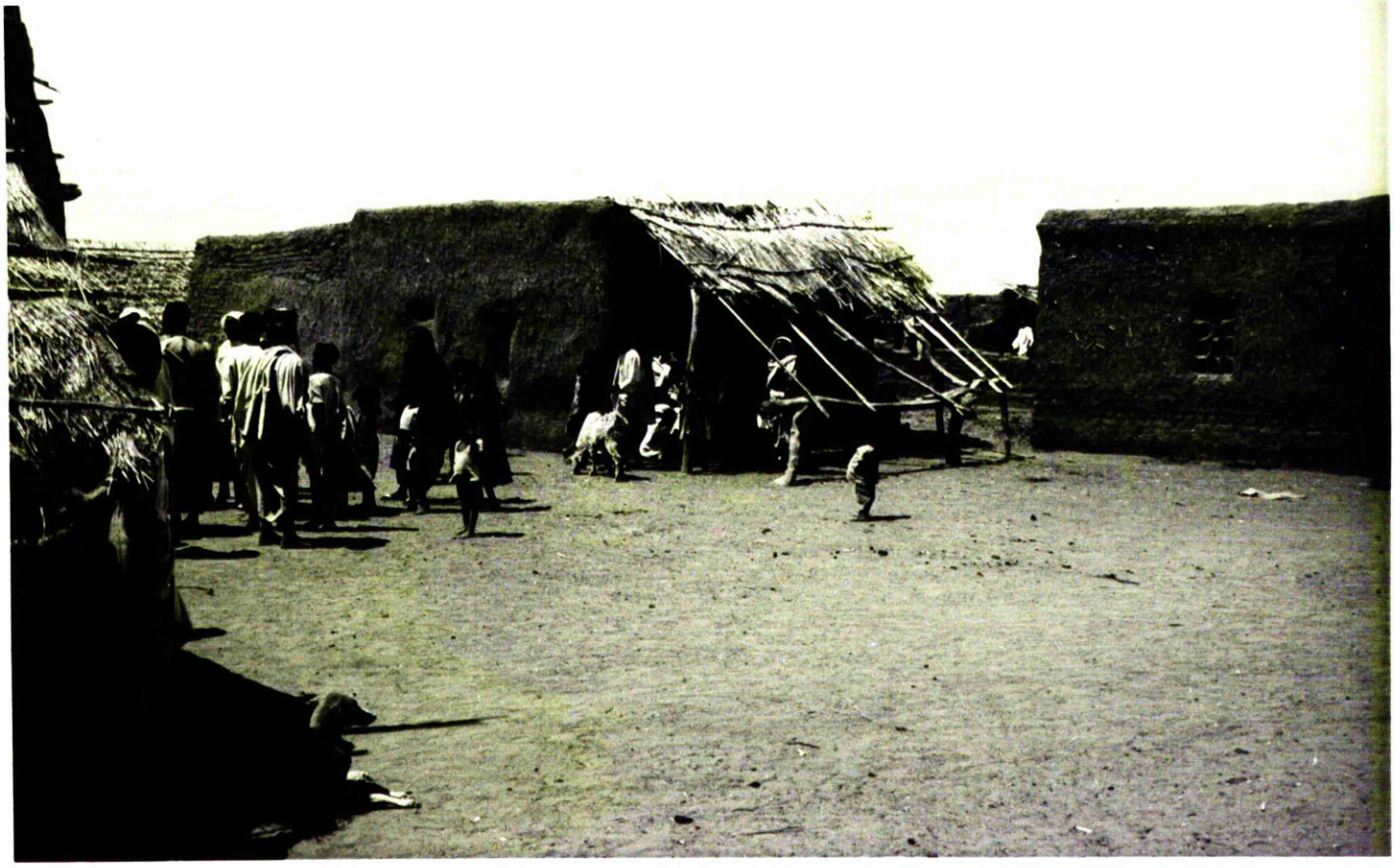


Fig. 20. THE VILLAGE HOUSE.

Fig. 21. SAMPLES TAKEN FROM THESE VILLAGERS.

A. flavus was the most common species of Aspergillus found in soil of groundnut fields and the authors state that it was present in every location investigated. As with our series, A. niger and A. nidulans were also very common and A. fumigatus isolates were rare. The climates of the two regions, Israel and North Sudan, differ in a number of respects and factors other than the most obvious one, must play a role in the distribution pattern of A. fumigatus and A. flavus. Nicot (1960) found A. fumigatus to predominate in a zone of Sahara soil. There is, at present, little information on this aspect and both are ubiquitous species. Raper and Fennel (1965) state that A. flavus is regularly isolated from soils, particularly those from tropical and sub-tropical areas and that A. fumigatus is abundant in soils. Both occur on decaying vegetation, including forage, and on stored seeds and grain and Austwick (1965) has postulated that it is on such substrates that the high spore production takes place which constitutes the infection hazard. The vegetable substrates are infected from the soil.

RESULTS.

A portion of the material obtained at surgical intervention was inoculated in Khartoum on agar media in universal containers and forwarded by air to Glasgow. In one instance no fungi were isolated and this case was subsequently found by histology to be neoplastic and not to be of mycotic origin. Mention is made of this because it is corroborative evidence that the fungi isolated from material from two of the cases detailed above (Cases 5 and 6) were unlikely to be casual contaminants. These isolates were identified as belonging to the Aspergillus flavus-oryzae group (See Fig. 22). One isolate was deep yellow-green and the other white with yellow-green sectors, but on the basis that the majority of sporing heads bore only a single row of sterigmata they were both assigned to A. oryzae in accordance with the Manual of Aspergilli (Thom and Raper, 1965). In the most recent monograph The Genus Aspergillus (Raper and Fennel, 1965) the members of the variable group of A. flavus-oryzae have been reclassified and separation on the basis of the number of

SPECIMENS FROM KHARTOUM

Date Received	Lab. No.	Isolate	Remarks
13/11/65	BP 298	Negative	(R) antral tissue negative histology
30/11/65	BP 303	Aspergillus flavus-oryzae (white and green sectors)	Case 5 Aged 28 positive histology
8/12/65	BP 305	A. flavus-oryzae	Case 6 positive histology
11/1/66	BP 314	A. flavus-oryzae (also A. niger, A. nidulans)	Case 6 - 10 days post-op.
21/1/66	BP 318	A. flavus-oryzae (but mainly A. niger)	Case 4 nasal swab - previously proptosis and cheek swelling
21/1/66	BP 319	A. flavus-oryzae	Case 6 nasal swab after surgery - clinically normal
15/2/66	BP 323	A. niger	Otitis media
15/2/66	BP 324	A. flavus-oryzae	Case 2 after surgery clinically normal

Fig. 22.

rows of sterigmata has been assigned much less significance. Further study of the isolates was, therefore, undertaken and the following characteristics were noted. Since the white and yellow-green sectors of the second isolate were found to breed true these were studied separately.

Isolate 1 (B.P.305 - Case No. 6)

This isolate makes poor growth on Czapek's agar which is a characteristic of Aspergillus zonatus (Kwon and Fennell). However, it fails to show the characteristic zonal growth on malt extract and although double sterigmata are not absent, heads with a single series of sterigmata predominate. In many respects it conforms to A. parasiticus but the conidia are not coarsely echinulate as in this species. (See Fig. 23).

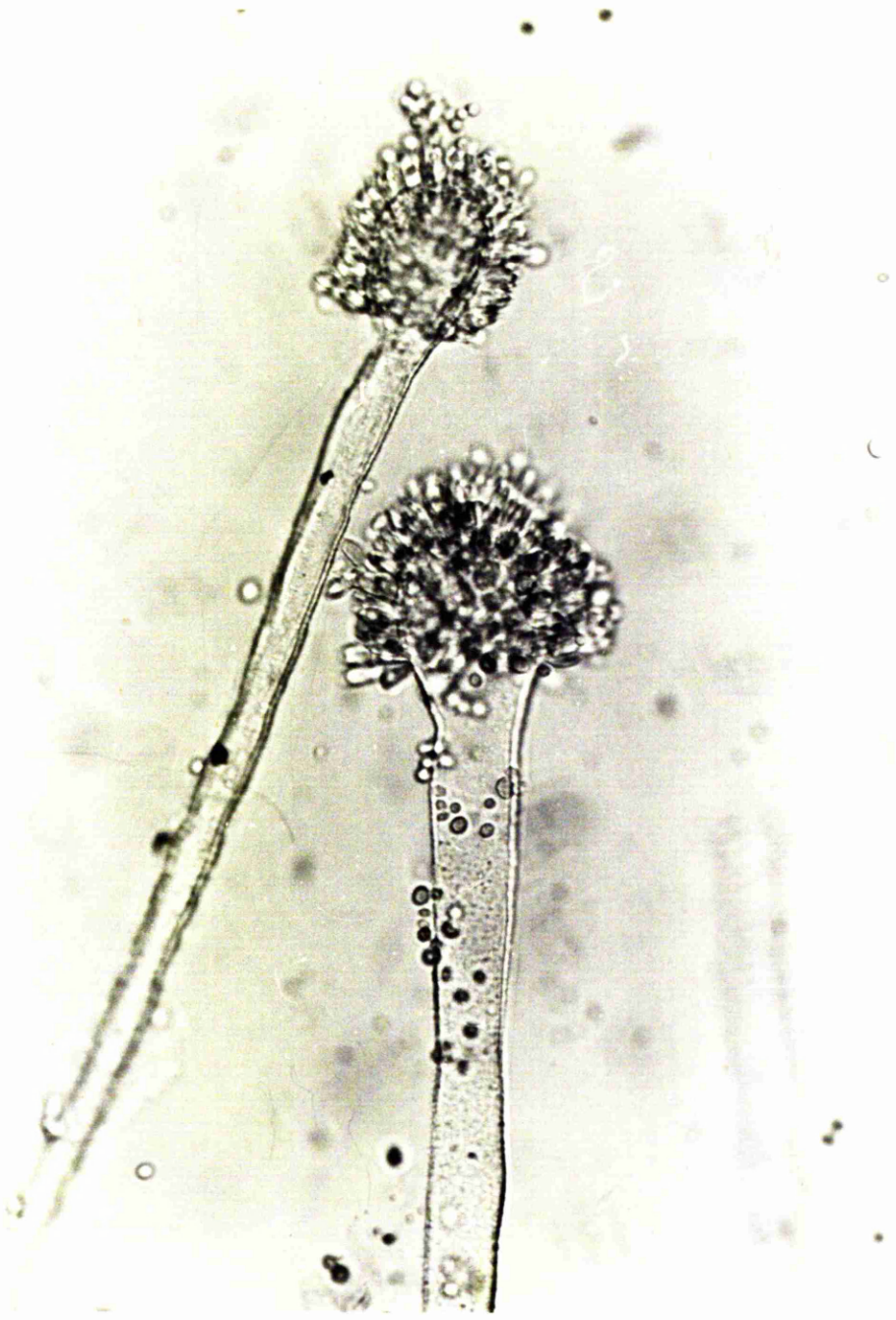


Fig. 23. B.P. 305 x 625. Aspergillus flavus showing sporing heads and single row of sterigmata - also rough conidiophores.

Isolate 2 (B.P. 303 - Case No. 5)

The two variants differ only in colour. Their form of growth on Czapek and malt extract agars and the dimensions of their sporophores etc. are alike. The white sectors are therefore considered as mutant forms of the normal green. The dimensions and/or form of the various structures do not conform with any of the species within the group which are described as having a single series of sterigmata and a reappraisal of this characteristic was therefore made. The majority of sporing heads were found to bear a double series of sterigmata and the isolates thus may be designated as Aspergillus flavus Link. It is possible that the primary isolates were abnormal in respect of sterigmata formation but the possibility of faulty observation is not excluded. (See Fig. 24).

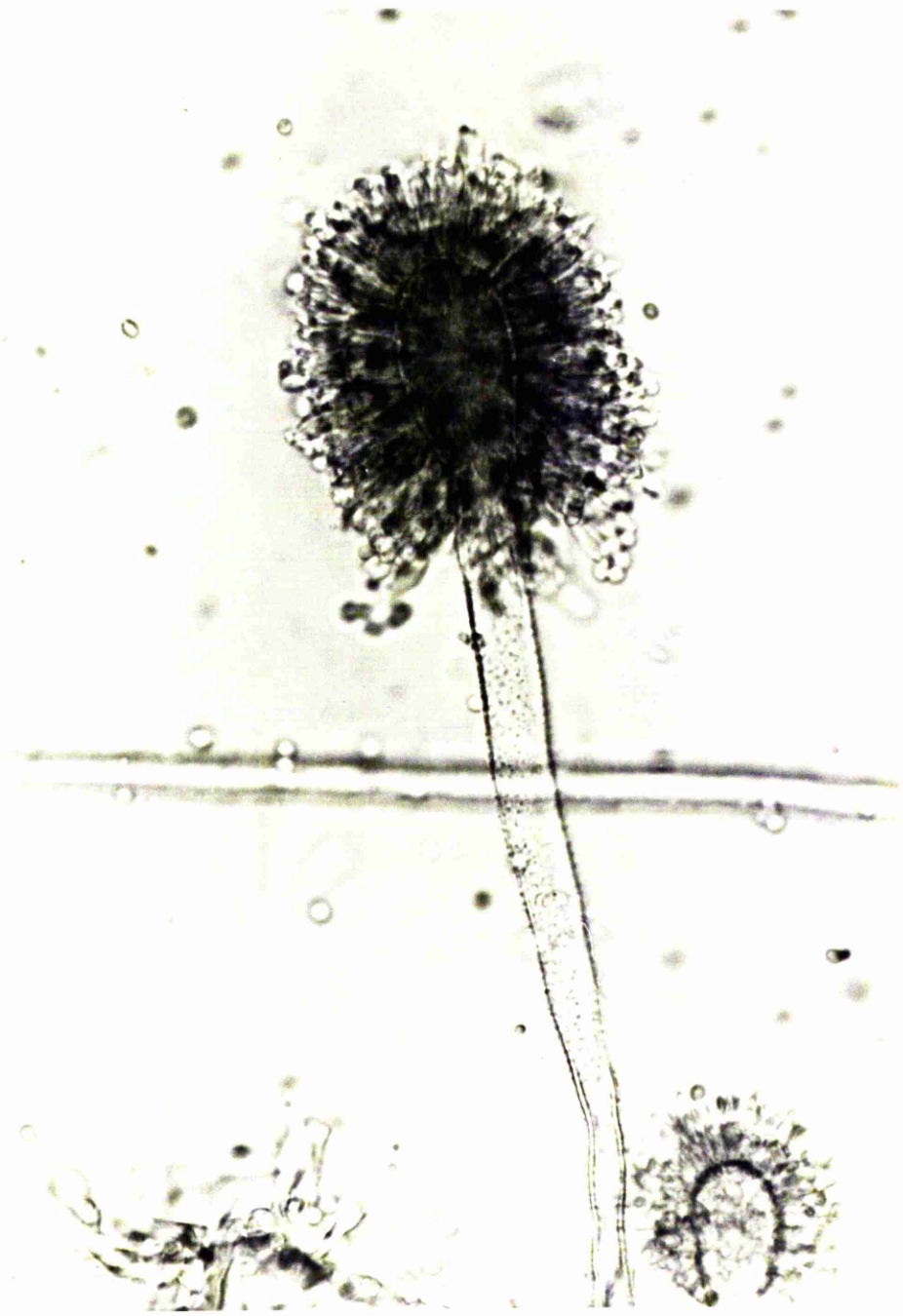


Fig. 24. B.P. 303 x 625. Aspergillus flavus showing roughened conidiophores and double row of sterigmata.

GENERAL

A number of the many isolates obtained from the environment (See Fig. 27) and nasal swabs (See Fig. 28) have also been examined and have been found to belong to A. flavus Link. One from a nasal swab formed sclerotia in the first few subcultures but has now ceased to do so.

It would seem not improbable that during their parasitic life the isolates from the patients underwent mutation, in the case of a biochemical nature and in the other a colour change. In view of this and their present characteristics it seems reasonable to assign both isolates to Aspergillus flavus Link.

Cultures have been sent to Professor K. B. Raper for opinion and others will be deposited in the Mycological Reference Laboratory, London School of Hygiene and Tropical Medicine. (See Fig. 25 & 26).

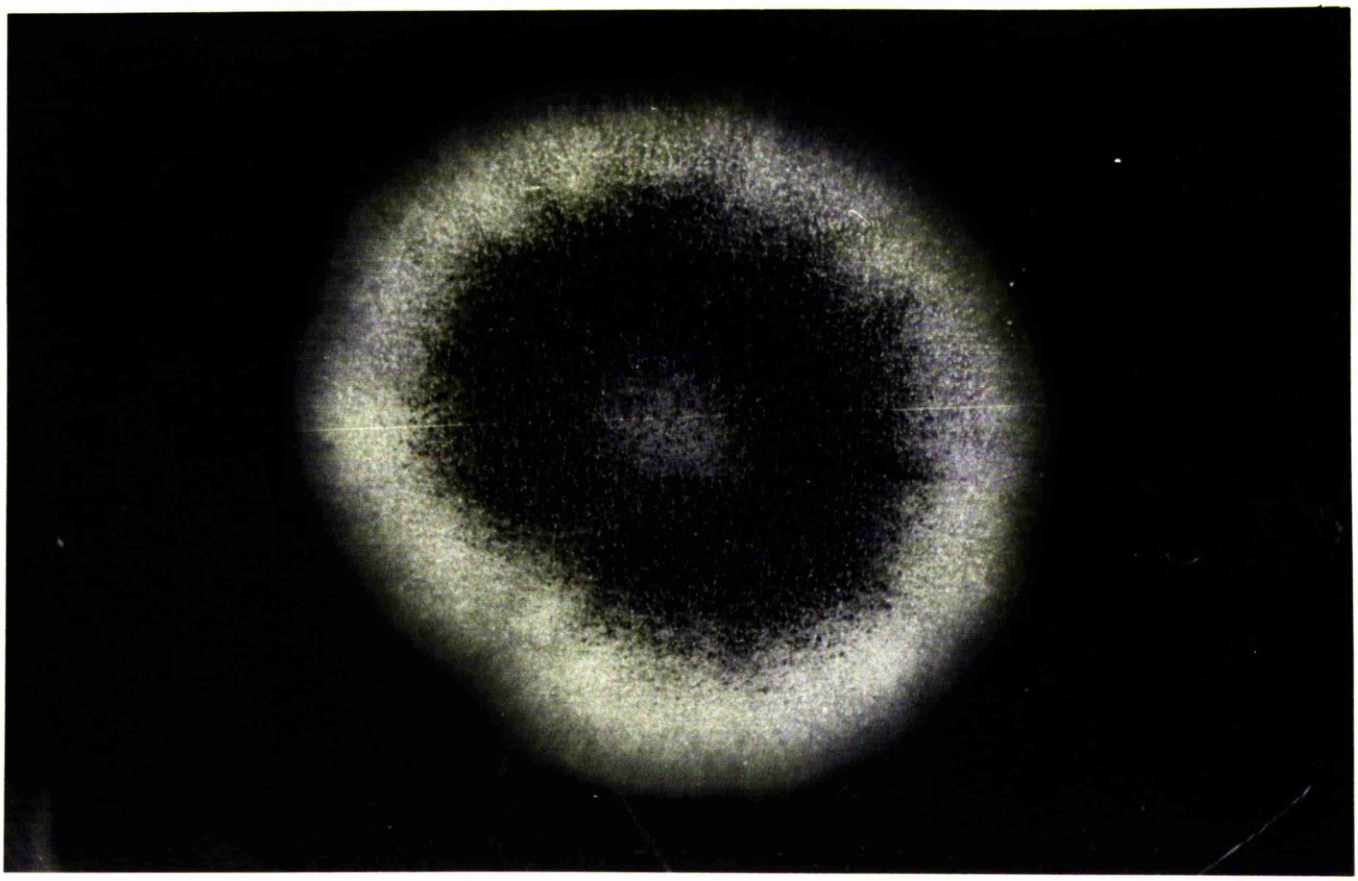


Fig. 25. B.P. 303 x 3 approx. Normal green sector in 8 day colony.

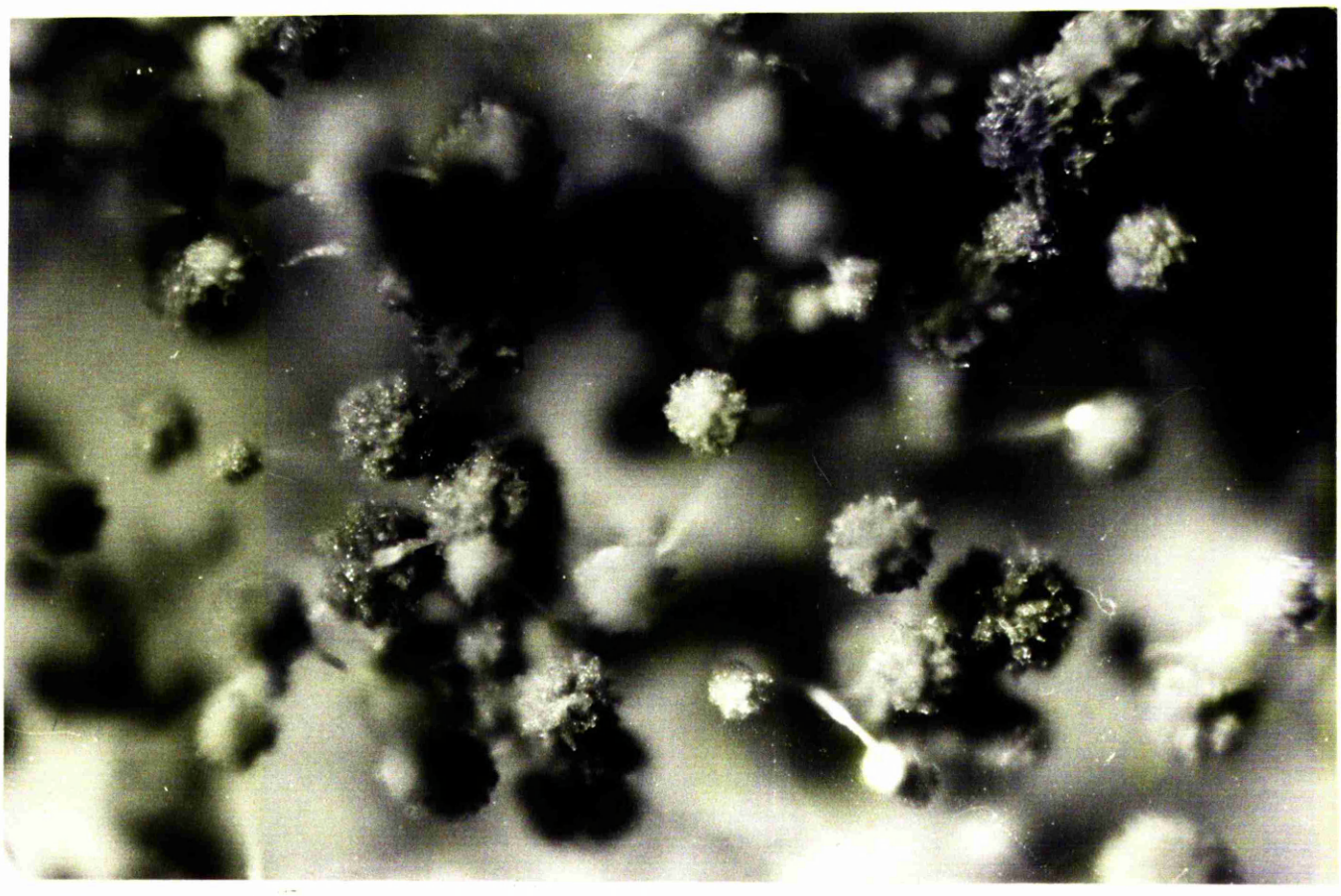


Fig. 26. B.P. 303 x 100 approx. Close up of colony showing sporing heads.

Sample	Investigational Method	Number of colonies isolated			
		A. flavus-oryzae	Other aspergilli		Other fungi
Dura	Dry	3	-		2
	Dilution series	56	3	(A. niger)	4
Dust from earth floor	Dilution series	52	24	(19 A. niger) (2 A. nidulans) (2 A. terrens) (1 Aspergillus sp.)	4
Cobwebs from roof	Dry	3	3	(A. niger)	1
	Dilution series	8	27	(22. A. niger) (5 A. nidulans)	-
Straw from roof	Dry	1	3	(A. niger)	-
	Dilution series	1	7	(A. nidulans)	1
Cotton from mattress and pillows of bed	Dry	-	1	(A. niger)	
	Dilution series	6	15	(9 A. niger) (6 A. nidulans)	3
Rope from bed	Dry	-	2	(A. nidulans)	-
	Dilution series	1	2	(A. niger) (A. nidulans)	-
Timber of house supports	Dry	2	-		1
	Dilution series	1	6	(A. niger)	2
Sheepskin	Dilution series	-	1	(A. niger)	1
Flour from Dura	Dry	3	-		1
	Dilution series	15	4	(2 A. niger) (1 A. nidulans) (1 A. terrens)	2
Snuff	Dry	-	-		-
	Dilution series	-	-		-
Earth from outside house	Dry	-	-		-
	Dilution series	41	7	(3 A. niger) (3 A. nidulans) (1 A. terrens)	3
Totals		193	105		25

Fig. 27. Samples from a Village House.

Isolates from Villagers

(Specimens received 7/3/66)

Source	No. of samples	Fungi		
		Aspergillus flavus-oryzae	Other Aspergilli	Other fungi
Nose	16	4	10 (A. niger - 6; A. nidulans - 2; A. terreus - 2)	7*
Throat	9	3	1 (Aspergillus sp.)	1+
Ear	1	1	-	-
Totals	26	8	11	8

* 2 Penicillium spp.
2 Curvularia s pp.
1 Cladosporium sp.
1 Helminthosporium sp.
1 Papulaspora sp.

\+ nonsporing

Fig. 28.

It is well known that the aspergillus is ubiquitous and commonly found in the tropics and subtropics associated with decaying vegetation; stored seeds, grains and various types of food products. It therefore seemed important to ascertain the frequency with which one could isolate aspergillus from the nose and nasopharynx of otherwise healthy people. I visited a village approximately one hundred and fifty miles into the desert where one of our patients lived and swabbed the nasal passages and throats from a random collection of villagers. The results of the cultures are shown in Fig. 28. These results, although small in number demonstrate that the presence of aspergillus in the nose or nasopharynx may be inconsequential per se. I believe that this opinion is substantiated by the culture results in the three post operative isolates obtained from Case Numbers 2, 4 and 6. These positive cultures were taken from clinically normal antra with no evidence of granulomatous disease in which free drainage had been established. In an attempt to localise the infective source the contents of a village house were

sampled from one room for culture and the results are shown in Fig. 27. These results are interesting in that they show a higher concentration of colonies from material inside the house than from outside where the animals live. Although many species of aspergillus were isolated, as well as other fungi, the greatest number of colonies were Aspergillus flavus-oryzae, the type cultured from the granulomata. "Dura" which produced the largest number of colonies is millet from which bread is made and it may be stored in the house for eight months or more.

The aetiology of aspergilloma is unknown and until now no large human series on the incidence of aspergillus in cases of chronic sinusitis has been reported. I think the incidence of aspergillus in the nose and nasopharynx in different parts of the Sudan might, by plotting the results, help us to discover the aetiology of this disease. So far none of our six cases occurred in people emanating from the Southern Sudan.

There is no doubt from the specimen cultures in the village house that aspergillus in its many forms is

abundantly present in the environment of these people and for that matter even in the throat and nose of many villagers but only one confirmed case of aspergilloma occurred in that village. One would have thought that the closed community village life as witnessed in these parts, associated with the storing of dura in the living room which comprises the house, might give a higher incidence of this disease. I think one must accept that all Sudanese in this region have at some time harboured aspergillus in their upper respiratory tract but have either not acquired a predisposing condition or have acquired an immunity to aspergillus. This also requires further and detailed investigation. The saprophytic and pathogenic status of aspergillus in the Sudan requires further investigation.

Radiography in the Sudan on 549 cases of pulmonary tuberculosis comprising 304 untreated cases and 245 treated cases did not show radiographic evidence of mycetoma in one case. It should be added that 348 cases out of the total of 549 had cavitatory disease. (Grande 1966)

Isolates from materials in house and surroundings of patient known to have had aspergillosis of the orbit.

Method:

In all but two cases the material was investigated both by inoculating small dry fragments of the substance on an agar medium (2% malt extract) and by plating out on the same medium serial dilution (1/10, 1/100, 1/1000) of an aqueous suspension of a portion of the sample. It was considered that the dry inocula would reveal A. flavus-oryzae if it was present in quantity (i.e. if it predominated or was present in a sufficient proportion of total mould content to develop to the stage of being identifiable before being overgrown by other moulds present). The dilution series would be likely to reveal its presence even if this was in small proportion compared to the quantity of other moulds in the material. For various reasons it was not found feasible to investigate the sheepskin or floor dust material by inoculation of dry specimen.

In view of the very varied nature of the samples no quantitative comparison between them can be made. (See Fig. 27).

DISCUSSION

Granuloma of the paranasal sinuses resulting in unilateral ocular proptosis and its sequelae is, according to the literature, a very rare condition. A retrospective review in Khartoum of histological reports and material which could be traced, suggested however, that non-specific granuloma of the paranasal sinuses in Northern Sudanese was in fact not so uncommon and on one occasion Professor Lynch had reported seeing mycelia and had questioned the possibility of Aspergillus. I found twenty-four related Biopsy Reports which might more than likely have been due to aspergilloma but they cannot be included here since the pathological specimens have been mislaid and are not available for re-examination.

I should not be making a novel observation if I said that far back in antiquity man realised that parasites were a cause of disease and that even before the clarifying advent of the microscope man believed that forms of life too small to be seen by the naked eye were also a cause of disease. But, without factual knowledge, he had to refer to them by such terms as "humors".

It is more than likely that the first report I have been able to find of a "fungus tumour" of the maxillary sinus causing unilateral ocular proptosis was, in fact, using the word "fungus" only as a descriptive term. The latter interpretation I think is confirmed by M. Plaignaud's report (1791) in which he describes a male patient of twenty-two years who complained of severe pain in the maxillary sinus following a contusion with disturbance of vision and projection of the eye. The "fungus tumour" of the "os mali" responded to repeated cautery allowing the patient to be discharged from hospital on the one hundred and thirty-fourth day with no evidence of residual disease. The diagnosis at that time was "Ozena" which translated from the Greek means "Stench". It was a disease of the nose with an offensive discharge and usually due to caries, rhinitis or syphylitic disease (Dorland 1946). Although Plaignaud named the lesion a "fungus tumour" I think he was really describing the appearance of a gumma rather than a neoplasm in view of the patient's age and probably <u>not</u> a mycotic lesion of the maxillary sinus. In the same year

Hernu described a case of "fungus" in the maxillary sinus who died and at post-mortem massive destruction was found but no histology was reported and I consider this to have been a neoplastic lesion.

In spite of Micheli's description of spore heads and stalks in 1729, a hundred years were to elapse before a firm diagnosis could be made of mycotic lesions. It was not until the work of De Bary in 1850 and in the same year Fresenius, Cramer, Wilhelm and Brefeld in Germany that an accurate diagnosis of fungus infection could be made (Raper and Fennell 1965). Although mycelia were recognised almost fifty years before the science of Bacteriology was pioneered by the monumental work of Pasteur and Koch in the nineteenth century; Mycology was to take second place because of the importance of such clamant scourges as plague, cholera and typhoid.

The casual observer even today would not be wrong if he believed that fungi are more often a benefit to man than a hazard. We depend on fungi to flavour cheese, ferment wine, produce antibiotics and organic compounds but with

the advancement of Medical Mycology and improved diagnostic facilities, fungi are more and more being recognised as a cause of disease in man. The recent finding of aflatoxin in Aspergillus fumigatus is only one example of the many possible dangers of fungal activity now known to man.

There have been several reports of Aspergillus being found or suspected as a cause of chronic nasal discharge and in a few instances associated with granuloma but in the main the reports have been on single cases and very few have been substantiated by culture of the fungus. In order to make a diagnosis of aspergilloma it is preferable to have a positive section stained by the periodic-acid/Schiff and methenamine silver methods, a positive culture and histological evidence of a granuloma.

In Berlin in 1891 Zarniko described an undoubted mycotic infection of the maxillary sinus by Aspergillus fumigatus in a fifty year old woman. The chief symptoms were difficulty in breathing through the nose and frontal headache. The nasal discharge was thick, foul smelling and greenish in colour. Some greyish-brown material the size of a pea

was removed and on microscopy a fungus was seen and thought to be Aspergillus fumigatus. No cultures were made and treatment was by frequent lavage and potassium iodide. This is usually taken to be the first authenticated case but five years earlier Schubert (1886) had reported a case from Nürnberg of aspergillosis of the nose in a seventy-five year old woman.

In 1894 Mackenzie working in Baltimore described a similar case in a thirty-five year old woman who for several years had a history of chronic suppurative infection of the right antrum associated with swelling of the right side of her face and base of nose. For two years she had repeated antral lavage with passage of shreds of false membrane. Some of this material was examined by Flexner at Johns Hopkins University who, using Weigert's fibrin stain, demonstrated mycelia which Dr. Lotsy diagnosed as those of Aspergillus fumigatus. MacKenzie believed that the fungus entered the sinus via the mouth.

Harmer (1912-13) reported a single case of mycosis in the maxillary sinus in a woman due to Aspergillus fumigatus

which was successfully cultured on blood agar at 37°C. The case was treated with several antiseptics plus potassium iodide which resulted in the discharge of a large membrane, following which the discharge ceased and the patient's condition improved.

Tilley (1914-15) reported that one of his cases formerly diagnosed as "endothelioma myxomatodes" of the maxillary antrum (Tilley 1909) had in fact proved to be a case of aspergillosis and that he had seen four other examples in adult women. In two patients both maxillary sinuses were involved and in one both ethmoids were also affected. All patients complained of nasal obstruction and discharge, sneezing, headache and pain around the cheek and eye. Cocaine produced little shrinkage of the pale oedematous mucosa (an observation which he regarded as of diagnostic importance) and transillumination revealed opacification. The Caldwell-Luc operation was successfully employed in all five patients permitting removal of semi-solid material of a pale greyish-blue colour loosely adherent to the walls of the sinus. Section by S. G. Shattock

of the material removed using the freezing microtome showed coarse mycelial filaments of appearance consistent with an Aspergillus sp. Tilley in a further review in 1915 emphasised the rarity of the condition; but stated that previous cases reported as "myxomas" of the maxillary sinus might well have been instances of aspergillosis. Tilley was unwilling to speculate on the aetiology but pointed out that his five patients were all adult females as was that of Harmer (1912-13). Tilley included in his paper a full copy of the report made by Shattock on the microscopy of the material obtained.

Harmer and Jockes (1918-19) reported a further case occurring in a thirty year old schoolmistress in which antral lavage produced a thick brown jelly like substance which on culture proved to contain an Aspergillus sp.

In none of these cases so far reported from the literature was there any indication that histological examination revealed a giant-cell granuloma. Tilley's description of removing semi-solid material might suggest that he was in fact removing a granuloma but histology did

not confirm this. Neither did the reports by Brown Kelly (1934), Nash (1938), Röhrt (1954), Montreuil (1955), Andersen and Stenderup (1956) and Savetsky and Waltner (1961) give any histological evidence that the fungus infection was associated with a granuloma.

Brown Kelly (1934) reported seven cases from Glasgow and he believed that aspergillosis in the nasal sinuses was not as uncommon as the textbooks suggested. He considered that cases were missed because the diagnosis was not considered and the symptoms misleading. In an attempt to aid the diagnosis he emphasised the significance of unilateral vasomotor rhinitis with paroxysmal sneezing and rhinorrhoea. The discharge of a membrane he felt was almost diagnostic of a fungus infection. It has been said by Wilson and Plunkett (1965) that the aspergillus is an opportunist and from my findings in the examination of a Northern Sudanese village, I believe, like Brown Kelly (1934), that conditions must be favourable, that is to say, provide shelter and stagnation of secretions to allow the aspergillus to become pathogenic. Shelter, I consider, is important because in Cases No. 2 and No. 6, although part of the mass

could not be removed, after adequate drainage was established the residual mass disappeared. Rhinorrhoea was not a feature of my cases but certainly Case No. 3, the student, who was probably my most vocal and reliable witness, complained of this. It is my belief that the hot dry climate (See Fig. 29) of the area in the Sudan where these six cases were found leads to encrustation in the nose and a high incidence of vasomotor rhinitis and consequent nasal polyposis and sinusitis. It would be very valuable to perform a series of nasal mucosal biopsies to see whether or not any epithelial metaplasia or atrophy occurs as a result of the local climatic conditions which would produce the favourable environment for aspergillus to become established.

In 1938 Nash reported a case of a forty-three year old woman who had a fulminating infection of the nose due either to monilia or aspergillus in which the left eye was destroyed by a necrotic mass which involved the left side of the nose, left ethmoid and left orbit. Biopsy revealed septate and branching mycelia; the organism was however, <u>not</u> cultured

CLIMATOLOGICAL NORMALS. KHARTOUM.

	JAN.	FEB.	MAR.	APR.	MAY	JUN.	JUL.	AUG.	SEP.	OCT.	NOV.	DEC.
Mean 24 hour Relative humidity % 1959 - 1962	29	21	19	19	19	30	50	59	44	31	29	32
Mean daily max. Temp. °C 1931 - 1960	32.1	33.7	37.2	40.4	41.9	41.5	37.9	35.9	38.2	39.6	36.2	32.7
Mean daily min. Temp. °C 1931 - 1960	15.7	16.6	19.5	22.8	25.9	26.8	25.6	24.8	25.4	25.1	20.9	17.0
Rainfall mm. 1931 - 1960	0	0	0	1	5	7	48	72	27	4	0	0

Fig. 29.

and so the final diagnosis is uncertain. The patient had severe diabetes mellitus and had lost much weight and Nash believed that this may have been related to the establishment of the mycosis.

It has been said by many that fungus infections are often associated with debilitating diseases (Raper and Fennell 1965) and that the increased incidence of opportunistic fungus infection is directly proportional to the increased use of steroids and cytotoxic drugs (Wilson and Plunkett, 1965). I was aware of these statements and so paid special attention to the general condition of my patients and made specific enquiry about steroids and antibiotics. Although diabetes mellitus is very common in parts of the Sudan I was unable to substantiate the belief that fungus infections were associated with this or any other systemic disease or with treatment by specific therapeutic agents.

Savetsky and Waltner (1961) also drew attention in their report of a case in a fifty-three year old negress, to the increase in opportunistic infection by fungi

accompanying the increased use of antibiotics, cytotoxic drugs and steroids and noted that there is a special affinity for the pulmonary system when local conditions are especially favourable, e.g. nose, ear or phthisical lung.

The cases reported by Röhrt (1954) from Sweden in a thirty-five year old and Montreuil (1955) in a thirty-four year old singer were similar to those previously recorded by Tilley (1914-15), Harmer (1912) and others.

Andersen and Stenderup (1956) described a further instance of maxillary sinus infection in a fifty-five year old Danish woman. There was a five year history of otitis media and of intermittent attacks of nasal obstruction and irritation, feeling of oppression, sneezing and nasal discharge. Large polyps were present in the left nostril and radiology showed massive blurring of the left maxillary sinus although the bone was not affected. The nasal polyps were removed and through a Caldwell-Luc approach the antrum and ethmoid cells on the left side were cleared of firm gelatinous material. Culture of the resected material gave a pure heavy growth of Aspergillus fumigatus.

Andersen and Stenderup believe that the sneezing, nasal stenosis and development of polypi were due to a local endogenous allergy in which aspergillus present in the nasal cavity and maxillary sinus acted as the allergen. An extract from the isolated aspergilli provoked a very strong cutaneous reaction but attempts at desensitisation failed. I believe that this is a very significant suggestion because in the histological sections of my cases plasma cells were much in evidence as were eosinophil polymorphs. The mechanisms which lead to blood or tissue eosinophilia are unknown although the association of these cells with hypersensitivity reactions is probably important. Supravital studies indicate an almost selective avidity of the cells for the ingestion of antigen-antibody complexes. (Dubos and Hirsch 1965). In my cases described above no circulating eosinophilia was found but histological sections of the granulomata showed tissue eosinophilia. There is also general agreement that the plasma cell and its precursors are the main cells responsible for antibody formation (Kallos and Waksman 1967). It has been postulated

by Pfeiffer that an endotoxin is released by the protoplasm of the fungus on its death and the recent finding of aflatoxin in Aspergillus fumigatus taken in conjunction with present histological findings do, I think, suggest a local allergic state which requires further investigation. An attempt to extract an endotoxin from the fungus plus peripheral blood examination in affected cases for specific antibody would, I believe, be of value.

I would again emphasize that none of the cases so far extracted from the literature gave any indication that histological examination revealed a giant-cell granuloma. The term "granulomatous inflammation" has come to be widely used in connection with tissue reactions to chronic infections of relative low virulence such as tuberculosis and fungus infection. The macrophages and giant-cells are important components along with varying numbers of lymphocytes, plasma cells and eosinophils.

Wright (1927) appears to have been the first to describe invasion of the orbit by aspergillus granulomas, although Delmeijer (1913) reported from Amsterdam the case of a

sixty-five year old patient with involvement of the orbit, cavernous sinus region and greater wing of the sphenoid due to Aspergillus fumigatus and Paterson (1915) in discussion on Tilley's paper "Aspergillosis of the maxillary antrum", an instance of involvement of the lacrimal sac. The aspergillus was thought to have entered the sac via the nose and the lacrimal duct. Wright's cases were a thirty-five year old man and a woman of unstated age. In the male proptosis, sinusitis and affection of the skin over the orbit were prominent. In the female, nodules were present under the skin, above and below the right internal tarsal ligament, and there was chronic dacryocystitis. In both cases there were bony changes; these were more severe in the male where the inner wall and roof of the left orbit were partially destroyed. Potassium iodide was administered to the male patient without improvement. Radiotherapy appeared to produce temporary alleviation in the male but in the case of the woman there was no effect.

Biospy showed an infiltrate of polymorphs, macrophages and giant-cells containing septate mycelial elements; the

latter were not clearly seen in conventional haematoxylin and eosin sections but were demonstrated with Leishman's stain. Cultures revealed pure growths of aspergillus. In a later note (Wright 1930) the results of detailed cultures made by H. W. Acton were reported. The first proved to be an Aspergillus oryzae and the second Aspergillus flavus type.

There is, I think, no doubt that the apparent rarity of this condition is in part due to the lack of awareness of such a specific granuloma and also the failure by other workers to recognise the significance of the negative staining bands within the giant-cells. Like Wright (1927) I consider it very difficult to make the diagnosis on routinely stained haemalum and eosin stained sections nor for that matter do I find Leishman's stain very helpful; I prefer to use the periodic-acid Schiff or silver methenamine methods to visualise the hyphae and make an accurate diagnosis of aspergilloma. The portal of entry is still unknown but I feel certain that it is through the nose but in some of my cases I had a definite history of

the whole condition starting as an itchy skin nodule (Cases 1 and 5) and in one of Wright's cases skin involvement is noted. It seems reasonable to assume that a fungus so readily available in the environment of the Northern Sudanese and present in many normal nasal passages should enter from this location rather than intradermally but here again further investigation is required.

Adam (1933) reported a case in a thirty-two year old negress, who showed left ocular proptosis and swelling of the left side of the nose with nasal discharge. There was involvement of the ethmoid, sphenoid and maxillary sinuses extending into the left orbit. Left ethmoidal biopsy showed fibrous tissue with giant-cells which contained refractile bodies. Staining by Gram's method revealed branched mycelial bodies and the culture grew Aspergillus fumigatus. Treatment was by surgery and administration of potassium iodide in doses increasing up to 200 grains daily.

Veirs and Davis (1958) pointed out that while fungus

infections of the globe of the eye are rather common, those of the orbit are rare. They reported four cases of ocular mycosis. One was an orbital actinomycosis, two were corneal mycosis, while the fourth was the forty-two year old wife of a farmer who had shown evidence for several months of an orbital mass. Radiology revealed clouding of the right frontal, ethmoid and maxillary sinuses. At operation an indurated granulation tissue mass replaced the orbital fat and there was destruction of the bone which separates the orbit from the frontal and ethmoid sinuses.

Microscopy showed fibrous tissue with numerous septate hyphae morphologically resembling an aspergillus but cultures were not made. Antral washings did not contain aspergillus. The patient improved on penicillin and sulphonamide therapy but no follow up report is given.

Veirs and Davis divide orbital mycosis into two groups: firstly non-granulomatous lesions which may show only draining sinuses and secondly, granulomatous lesions which produce proptosis and limitation of eye movement. I do

not consider that this is a useful classification because as I have already said aspergillus is ubiquitous and I am certain if looked for in all cases of chronic nasal affections would be present in a very high proportion of cases and probably of no significance in the majority. Similarly I do not agree, in our present state of knowledge of the presence of aspergillus in the nose and nasopharynx, with the classification of Hora (1965) as invasive and non-invasive. I have divided the six cases presented in this thesis into a purely anatomical classification of a) Ethmoido-orbital, Cases 1 and 6, and b) maxillo-orbital, Cases 2, 3, 4 and 5, but this division is related purely to aspergilloma. I think it is important in all cases of chronic recurrent refractory sinusitis that a thorough search should be made for aspergillus which is resistant to our present armamentarium of antibiotics.

It is my belief that the success in the treatment of the cases presented was due entirely to adequate drainage which amounted to complete communication between the affected sinus, the nose and nasopharynx. In the case

of the maxillary sinus this may be achieved by complete removal of the medial and posterior walls of the antrum and in the ethmoidal sinus by removal of the floor. Failure to achieve this end will result in such a case as that reported by Weller, Joseph and Hora (1960). They reported in detail the case of a thirty-one year old negro soldier who had served in Korea, Japan and Texas. There was proptosis of the right eye, while radiological examination showed increased density of the upper half of the maxillary sinus and haziness of the inferior ethmoid cells on the right side. A biopsy from the right maxillary sinus was diagnosed as non-specific granuloma and therapy with penicillin, terramycin, I.N.A.H. and streptomycin was commenced. There was no improvement and a Caldwell-Luc operation was performed. Material obtained from the right maxillary sinus showed fungus elements in sections stained by the periodic-acid/Schiff method, while culture produced a growth of Aspergillus flavus. As much as possible of the granuloma was removed, the orbital floor was found to be eroded with loss of

demarcation between the granuloma and the structures of the orbital floor. Potassium iodide, nystatin and amphotericin β were used at various times with little improvement. Eighteen months later the right orbit was explored and a fibrous mass in the inferior part was removed piecemeal. This proved to be an aspergilloma. Six months later further surgery was performed on the sinus but soon after swelling appeared above and anterior to the right ear. One year later a still further operation revealed granuloma below and lateral to the globe, extending to the orbital apex and into the pterygo-maxillary space. As much as possible was removed and the orbit was decompressed superiorly, medially and laterally. Histology showed giant cells and hyphae: Aspergillus flavus was cultured. Proptosis however recurred ten months later.

Although the granuloma was removed as vigorously and completely as possible, at no time is any suggestion made of an attempt to drain the sinus. This I consider to be a quite essential part of treatment.

Bailey and Fulmer (1961) noted that at that time only five cases of orbital aspergilloma were on record including Tikomirov's (1958) case from Russia of an orbital mycosis simulating a malignant neoplasm. Theyreported a further case in a sixty-five year old male cotton gin worker who presented with right sided proptosis. The antrum and orbit were involved in a chronic granulomatous process. Biopsy material from the antrum showed septate mycelia with some attempt at spore formation. A second specimen was cultured and Aspergillus flavus was grown.

Treatment with amphotericin β in doses up to 70 mgm/day produced little effect but oral potassium iodide given in 40 drop doses thrice daily for eight months produced some subjective improvement. Griseofulvin given in divided doses orally up to 2.0 grams daily also gave some relief.

Bennett, et al (1962) in a paper on unusual inflammatory lesions of the face described a fifty year old woman with inflammation and deformity of tissues around the left eye. At the age of thirty-five years the patient had noted a growth involving the left lower eyelid and three years later this was partially excised along with the nasolacrimal apparatus.

Two years later, at the age of forty years, a Caldwell-Luc approach produced maxillary antral tissue. Four years later biopsy of the left infra orbital mass showed an aspergilloma due to Aspergillus fumigatus. This was treated with iodine, Gantrisin, radio-therapy and a vaccine prepared from the wound exudate. Within a year there was complete regression but soon afterwards a nodule appeared in the left lower eyelid which responded to Amphotericin β. Three years later a recurrence demanded radical exenteration of the orbit and no recurrence was noted one year thereafter. However, Hora later reports (1965) a recurrence in this case which responded again to Amphotericin β intravenously.

For effective treatment by antibiotics it is essential that firstly the drug should reach the lesion and secondly it should be present in the lesion at a concentration adequate to destroy the infecting organism. Riddell and Stewart (1958) said when discussing treatment of broncho-pulmonary aspergillosis that it is not surprising that the parenteral administration of antifungal

drugs is ineffective because the fungus lies beyond the reach of agents from the blood stream - for example, in the lumen of a bronchus or cyst.

The histological appearances of the granulomata showed a large amount of fibrous tissue and at the time of surgery was in itself a relatively avascular mass. Organisms of phycomycosis and aspergillosis are known to invade arteries and veins producing infarcts (Anderson 1966) so that the combination of steroids plus antibiotics in the early stages of this lesion may be the treatment of choice.

It is true to say that not only the cases presented in this study but also those culled from the literature have a long history with non-specific symptoms but a more energetic search for aspergillus in refractory cases of sinusitis might enable the condition to be arrested before granulomatous inflammation becomes established. I believe however, that even in the early stages of this infection a Caldwell-Luc operation (Scott-Brown et al 1965) combined with wide drainage to the nose, must be performed

to obtain good results. In all the cases reported polytherapy has been used and the long term results have not been good. Amphotericin β in some instances seemed to be beneficial but this drug was never given alone and recurrences with this treatment were usual. Potassium iodide appears to be the effective drug but it is by no means certain to be curative. It is possible that the iodoform pack which was used routinely in my cases played some part in the local destruction of the fungus but I am certain that wide drainage was the main reason for the good results obtained. Radio-therapy does not appear to have anything to offer and it is difficult to see any rationale for its employment.

The six cases presented in this thesis were all male but this is probably not significant because at this time in the Sudan the inferior status of women is such that male attendance at hospital is far in excess of female. There is no clear sex preponderance in the cases so far culled from the literature.

The first five cases reported in this thesis were

lesions on the left side and so the possibility of a local anatomical defect was considered but nothing to substantiate this belief was found. Neither does the literature indicate that one side is more commonly affected than the other.

CONCLUSIONS

From Northern Sudan a series of six cases has been presented to elucidate a recently recognised specific granuloma which affects the paranasal sinuses and causes unilateral ocular proptosis. In many respects the granuloma behaves like a locally malignant condition causing severe tissue destruction, including that of bone. A surgical approach to this disease has been described which is at present the only satisfactory treatment. A complete review of the world literature has been incorporated with a review of the present status of antifungal drugs in the treatment of this lesion. Small but relevant investigations on the environment of this aspergilloma are reported and significant observations have been made. Suggestions are given concerning further research requiring to be done.

"Epidemiology" is derived from the Greek words epi (upon) demos (people) and logos (study of). Thus from its derivation, "epidemiology" implies the study of what "falls upon people". During the passage of time

however, it has come to mean aetiology of all diseases including non-communicable ones. It is of interest, however, that more recently the work of Burkitt (1966) on the geographical distribution of disease in East Africa forces us to return to the original derivation of the word "Epidemiology" and re-emphasize man's environment. It is my belief that aspergilloma is an example of disease resulting from Man's environment and is not uncommon in parts of the Sudan because of the climate and the way of life of the people.

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