and anorexia; calcium deposits or band keratitis may be seen in the eye; isosthenuria, albuminuria, and renal failure are the inevitable outcome, irrespective of the cause.

This clinical syndrome occurs in hyperparathyroidism (Mellgren, 1943; Albright and Reifenstein, 1948). Bradlow and Segel (1956) collected seven cases with acute onset, of which only their patient survived; it was their paper which led us to the exploration of the neck, as delay has been fatal in a potentially curable disease. All these cases had long-standing symptoms of bone or renal disease and may be regarded as "acute on chronic." The syndrome also occurs in myelomatosis (Albright and Reifenstein, 1948), carcinomatosis (Gutman *et al.*, 1936), vitamin D, calciferol, or "A.T. 10" overdosage or sensitivity (Tumulty and Howard, 1942; Danowski *et al.*, 1945), sarcoid (Anderson *et al.*, 1954), the milk-alkali syndrome (Burnett *et al.*, 1949), idiopathic hypercalcaemia of children (Schlesinger *et al.*, 1956), and on immobilization, especially of children, with poliomyelitis (Albright *et al.*, 1941), and fractures (*Ann. intern. Med.*, 1942); it has also been produced by accidental "parathormone" overdosage (Lowenburg and Ginsburg, 1932) and experimentally in animals (Collip, 1925). All these cases show similar features.

In malignant disease, it is thought that bone destruction releases calcium into the circulation. This is only a partial explanation, as the presence of hypercalcaemia does not depend on the extent of the metastases (Gutman *et al.*, 1936; Baker, 1956). Such cases are likely to be seen more often because hormone treatment of carcinoma of the breast may raise the serum calcium (Herrmann *et al.*, 1949; Baker, 1956). Furthermore, cases have now been described in which there is hypercalcaemia when careful post-mortem examination has shown no secondaries in bone (Connor *et al.*, 1956; Plimpton and Gellhorn, 1956). In all these malignant conditions the inorganic phosphate is usually normal or high, but a number of cases have been described in which, as in this case, it was low. Diagnosis may be very difficult, but it seems that the cortisone test is a valuable and rapid means of distinction from hyperparathyroidism, which is the most important differential diagnosis; it has proved ineffective in some cases of carcinomatosis (Plimpton and Gellhorn, 1956). A survey of reported cases suggests that a rapid onset of the syndrome of hypercalcaemia is especially common in malignant disease (Swyer *et al.*, 1950).

The treatment is that of the underlying disease, but Albright and Reifenstein point out that a calcium of 17 mg./100 ml. is the danger point, and, in hyperparathyroidism at least, treatment to prevent death from calcium intoxication before operation is vitally important. In the main, restriction of calcium in the diet and high fluid intake, intravenously if necessary, are all that are required or, indeed, possible. This is an urgent matter and to delay may prove fatal. Symptoms of calcium intoxication can be relieved in most cases of myelomatosis, carcinomatosis (Plimpton and Gellhorn, 1956), sarcoid (Anderson *et al.*, 1954), and hypercalcaemia of children (Creery and McNeill, 1954), by cortisone, and this drug is a valuable form of symptomatic treatment in these circumstances, as well as prolonging life and providing a useful diagnostic test. Sodium citrate and sodium "versenate" (E.D.T.A.) are generally ineffective.

Summary

The clinical course is described of a man aged 49 who presented with features of hypercalcaemia of rapid onset. Necropsy showed carcinomatosis, but there was no sign of bone metastases. The hypercalcaemia was temporarily controlled with cortisone.

I thank Dr. D. Stern for carrying out the necropsy; the resident staff and nurses for their untiring efforts in the care of this patient; and Professor Dent for valuable advice in his management.

REFERENCES

Albright, F., Burnett, C. H., Cope, O., and Parson, W. (1941). *J. clin. Endocr.*, **1**, 711.

—— and Reifenstein, E. C. (1948). *The Parathyroid Glands and Metabolic Bone Disease*. Williams and Wilkins, Baltimore.

Anderson, J., Dent, C. E., Harper, C., and Philpot, G. R. (1954). *Lancet*, **2**, 720.

Ann. intern. Med., 1942, **16**, 176.

Baker, W. H. (1956). *Amer. J. Med.*, **21**, 714.

Bradlow, B. A., and Segel, N. (1956). *Brit. med. J.*, **2**, 197.

Burnett, C. H., Commons, R. R., Albright, F., and Howard, J. E. (1949) *New Engl. J. Med.*, **240**, 787.

Collip, J. B. (1925). *Ann. clin. Med.*, **4**, 219.

Conner, T. B., Thomas, W. C., and Howard, J. E. (1956). *J. clin. Invest.*, **35**, 697.

Creery, R. D. G., and McNeill, D. W. (1954). *Lancet*, **2**, 110.

Danowski, T. S., Winkler, A. W., and Peters, J. P. (1945). *Ann. intern. Med.*, **23**, 22.

Gutman, A. B., Tyson, T. L., and Gutman, E. B. (1936). *Arch. intern. Med.*, **57**, 379.

Herrmann, J. B., Kirsten, E., and Krakauer, J. S. (1949). *J. clin. Endocr.*, **9**, 1.

Lowenburg, H., and Ginsburg, T. M. (1932). *J. Amer. med. Ass.*, **99**, 1166.

Mellgren, J. (1943). *Acta path. scand.*, **20**, 693.

Plimpton, C. H., and Gellhorn, A. (1956). *Amer. J. Med.*, **21**, 750.

Schlesinger, B. E., Butler, N. R., and Black, J. A. (1956). *Brit. med. J.*, **1**, 127.

Swyer, A. J., Berger, J. S., Gordon, H. M., and Laszlo, D. (1950). *Amer. J. Med.*, **8**, 724.

Tumulty, P. A., and Howard, J. E. (1942). *J. Amer. med. Ass.*, **119**, 233.

MUCORMYCOTIC GRANULOMA POSSIBLY DUE TO *BASIDIOBOLUS RANARUM*

BY

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This paper is about an unusual case in which biopsy of a subcutaneous mass showed a granuloma containing mycelium of a fungus which, though cultures were not obtained, was thought possibly to be *Basidiobolus ranarum*, one of the rarest causes of mucormycosis. This interpretation was made because of the similar findings by Joe, Eng, Pohan, van der Meulen, and Emmons (1956) in Djakarta in specimens from comparable but more extensive granulomas in two Indonesian children: in one of their cases they isolated a fungus which Emmons identified as *B. ranarum*. The patient whose case is recorded below seems also to have acquired her infection in Indonesia, and this common geographical factor, together with the similarity of the clinical observations and the apparently identical histological findings, is thought to justify the conclusion that the three cases may be of the same nature.

Joe *et al.* (1956) appear to be the only authors who have identified *B. ranarum* with certainty as the cause of human infection. They mentioned two other reports in which infection had been attributed to this organism. One, from the East Indies, concerned a horse (van Overeem, 1925), and the other, from Istria, a gastric

ulcer in a man (Casagrandi, 1931). The case of supposed human infection is very questionable; the infection of the horse took the form of a chronic suppurating granulomatous lesion with a discharging sinus—the lesion was excised and an organism which was thought to be *B. ranarum* was cultivated from it. Joe *et al.* (1956) commented on the pathological dissimilarities between these cases and their own two cases. As *B. ranarum* was isolated abundantly and in pure culture from two successive biopsy specimens in one of their cases there seems to be no doubt about the accuracy of their interpretation of its role as the cause of the lesion. The clinical and pathological similarity between that case and their second case seemed adequate justification for considering the latter to be of the same nature.

B. ranarum is ordinarily a saprophytic mould found in the intestinal contents in frogs and lizards, and in beetles which feed on their dung and which in turn are their prey. It has been identified in various parts of the world, including parts of Europe. It is one of the Phycomycetes, and infection caused by it is therefore considered to be a mucormycosis. In common with the other fungi which cause mucormycoses, *B. ranarum* is characterized by the production in the tissues of a broad infrequently branching mycelium which is without septa. In histological preparations the mycelial filaments often have an appearance reminiscent of lengths of creased ribbon or look like empty and partly collapsed tubules with transparent walls. These appearances, the large diameter of the hyphae, and the characteristic absence of septa enable the mucormycoses to be distinguished readily from other infections caused by myceliate fungi. However, the findings in sections do not enable one to go farther than recognize the presence of a mucormycosis: cultures are essential for the identification of the various species of fungi which cause the infections belonging to this group.

The Phycomycetes—the order to which the fungi which cause the mucorcycoses belong—are widespread in nature as saprophytes, usually on decaying organic matter. Infections by these organisms are infrequent: Hutter (1959) in a review of the world literature was able to find only 116 cases recorded in the hundred years' history of the mucormycoses, and the diagnosis was in doubt in about a fifth of these cases. Pathogenic species of Phycomycetes have so far been recognized in only three families—the Mucoraceae, Mortierellaceae, and Entomophthoraceae. The Mucoraceae are the most important, and include three pathogenic genera—*Absidia, Mucor,* and *Rhizopus*: most cases of deep-seated mucormycotic infection are caused by *Rhizopus oryzae.* The most important clinicopathological form of mucormycosis is cerebral infection, which occurs particularly as a complication of serious metabolic disturbances, especially poorly controlled diabetes mellitus. Cerebral mucormycosis is almost invariably mortal : it has recently been reviewed by Long and Weiss (1959). The only cases of visceral mucormycosis recorded in Britain have been of this type (Kurrein, 1954; Symmers and Plummer). There is some evidence that the incidence of at least one of the serious forms of mucormycosis—disseminated haematogenous infection—may be increasing as a result of the increase in the use of certain types of modern drugs (antibiotics and adrenal cortical steroids, and the drugs used in the chemotherapy of malignant diseases) (Zimmerman, 1955).

The case reported illustrates another variety of this rather complex group of fungal infections.

Case Report

The patient, a 13-year-old Dutch girl, was on holiday in London, staying with her grandparents. They went bathing with medical friends, who noticed a thickening of the tissues between her shoulder-blades. The child said that her mother had found this lump about five months earlier, while they were at sea shortly after leaving Indonesia, where she had lived for six years: until then she herself had not known that it was present, for it caused no symptoms. Nothing was done when the lesion was first noticed, and it got progressively smaller. When her English friends noticed it the patient estimated that it had shrunk by about a third.

On examination the lesion had an ill-defined edge but seemed to be about 5 cm. in diameter; it felt as if it was about 1.5 cm. thick at its centre. It could not be moved apart from the skin, which, however, was perfectly normal in appearance. The mass was to some extent movable over the underlying tissues, though there was clearly some fixation to them. The whole mass was uniformly firm in consistency, but not hard; it was only a little tender on firm pressure. The clinical diagnosis was fibroma or lipoma, but as the findings were not typical the possibility of sarcoma was considered and it was thought wise not to take the history of shrinkage of the lesion too seriously into account until the nature of the lesion had been investigated. It was therefore decided to explore the lesion, with a view to its excision.

At operation it proved to be a fibrous and fairly vascular mass, quite tough to cut, and fairly well demarcated from the adjoining subcutaneous tissue though inseparably merged with the overlying dermis. A small wedge was removed from the marginal part of the mass and fixed in formol-saline solution. Paraffin sections were examined on the next day and showed a mucormycotic granuloma (see below). Cultures could not be prepared from the biopsy specimen, and it was not felt justifiable to repeat the operation in order to get further material for cultivation. No discharge occurred from the wound, which healed quickly. No treatment of any sort was given. There was no clinical evidence of any disease elsewhere in the body. *X*-ray examination of the chest and of the nasal sinuses showed no abnormality. Haematological examination was normal and the erythrocyte sedimentation rate was not increased. The patient had no fever.

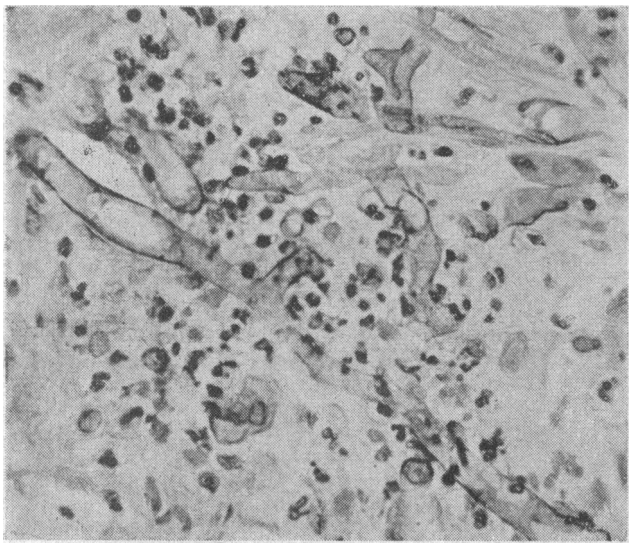
The lesion slowly got smaller and within four months of the operation had disappeared altogether. There has been no recurrence in the period of 18 months which has since passed.

Histological Findings

The biopsy specimen consisted of fibrotic granulomatous tissue containing occasional microabscesses and a scattering of foreign-body giant cells. There was a fairly abundant cellular infiltration, eosinophils being conspicuous in some areas; neutrophil polymorphonuclear leucocytes, lymphocytes, plasma cells, and macrophages were present in various proportions in different areas. The only specific feature about the granuloma was the presence of the hyphae of the fungus: they were not abundant, and only in one field (see accompanying Figure) were several seen together—elsewhere only single hyphae were found among the pus cells in microabscesses, or even occasionally in the cytoplasm of multinucleated giant cells. The hyphae had all the characteristics necessary for the identification of the organism as a member of the order Phycomycetes—their diameter ranged between 7 and 25 microns, they were thin-walled and unpigmented, and they appeared to be completely without septa.

As infection and thrombosis of blood-vessels is a striking feature of the lesions in many cases of the other forms of deep-seated mucormycosis, serial sections of this biopsy

specimen were searched for evidence of vascular involvement: some small thrombosed vessels were found in occasional areas of more active inflammation, but this seemed to be merely part of the inflammatory process in general, and no mycelium was seen in or near any of these vessels. The hyphae were quite readily seen in haematoxylin-eosin preparations, their thin walls being coloured pale blue by Mayer's haemalum: sometimes attention was drawn to their presence by a deposit of eosinophil matter on their surface, and sometimes by the way in which their



Broad non-septate mycelium typical of the fungi which cause mucormycosis: in granulation tissue in the biopsy specimen from the case described. Macrophages, neutrophil polymorphonuclears, and eosinophils are present in the cellular exudate. Periodic-acid/Schiff reaction; Mayer's haemalum. (×375.)

bulk displaced the cellular exudate in the little abscesses. The use of special staining methods added greatly to the ease of demonstrating the organism, particularly when cut across—the periodic-acid/Schiff reaction, Gridley's stain, and particularly Grocott's modification of the Gomori methenamine (hexamine)/silver-nitrate stain gave admirable results.

Comment

This case so closely resembled the two cases recorded by Joe *et al.* (1956) that their identity is scarcely open to question. All three patients were children, the other two being Indonesian boys, aged 4 and 8 years. All of them must have acquired the infection in Indonesia, though its source remains unknown. The lesion was a subcutaneous granuloma in each case, and started on the thorax; there was no history of injury or of any insect bite or the like, which might have been the means by which the organism entered the tissues. The disease was much less extensive in the girl's case than in either of the others: in one of the boys it spread for two years, eventually involving both axillae, both arms, the abdomen, and the buttocks. In all three cases there seems to have been no interference with the general health, and the condition eventually disappeared without any particular treatment being needed. The total duration was about nine months in the cases of the girl and of one of the boys, and over four years in the case of the other boy.

Though *B. ranarum* was isolated in only one of the three cases the evidence seems to justify considering all three to have been of the same nature, particularly in view of the common geographical background and of the virtually identical appearances of the organism and of the tissue reaction in the biopsy specimens from the three cases.

The observation of such a case in Britain is interesting in itself, but this should not obscure the fact that the case described must be regarded as an example of an exotic form of mucormycosis, very different in aetiology and prognosis from the cerebral infection which has been recognized as a naturally occurring, if rare, disease in this country.

Summary

A case of mucormycotic granuloma of the subcutaneous tissue is reported. The patient was a child who had lived in Indonesia until shortly before the lesion appeared. The diagnosis was made histologically. Though cultures were not obtained it is thought that the infection may have been caused by *Basidiobolus ranarum*, as this mould was isolated from one of two virtually identical cases studied in Indonesia by Joe *et al.* (1956).

The lesion disappeared without treatment after a total course of about nine months.

[ADDENDUM.—I am indebted to Dr. Lie Kian Joe, of the University of Indonesia, for information about two further cases of this infection in Indonesian children studied since he and his colleagues reported their first cases (Joe *et al.*, 1956). The clinical picture, pathological findings, and course in the new cases were similar to those originally described.

Dr. Joe and Dr. Chester W. Emmons have kindly allowed me to see sections of the biopsy specimens from their patients. The histological appearances are indistinguishable from those in the case described in this paper.]

REFERENCES

Casagrandi, C. (1931). *Riv. Biol.*, **13**, 1.
Hutter, R. V. P. (1959). *Cancer (Philad.)*, **12**, 330.
Joe, L. K., Eng, N.-I. T., Pohan, A., Meulen, H. van der, and Emmons, C. W. (1956). *A.M.A. Arch. Derm.*, **74**, 378.
Kurrein, F. (1954). *J. clin. Path.*, **7**, 141.
Long. E. L., and Weiss, D. L. (1959). *Amer. J. Med.*, **26**, 625.
Overeem, C. van (1925). *Bull. Jard. bot. Buitenz.* (Ser. 3), **7**, 423.
Symmers, W. St. C., and Plummer, N. S. To be published.
Zimmerman, L. E. (1955). *Amer. J. clin. Path.*, **25**, 46.

"When the vital statistics of the [fifties] are studied, the remarkable feature is that Aberdeen—never previously in the lead—stepped into first place and retained it. For example: the infant death rate tumbled from an average of 58 per thousand live births for 1940–9 to an average of 24 for 1950–9 (or from 1,790 baby deaths in 1940–9 to 772 in 1950–9), and in the last six years of the decade no Scottish city had in any single year a rate lower than Aberdeen's. The stillbirth rate fell from an average of 24 per thousand total births in 1947–9 to an average of 16 in 1957–9, and in every year of the decade the stillbirth rate was the lowest recorded in any of the cities. The total number of deaths at 1–5 years dropped from 333 in 1940–9 to 120 in 1950–9. The average age at death rose almost year by year from 57.3 in 1947 and 61.7 in 1948 to 67.3 in 1958 and 66.7 in 1959. The tuberculosis death rate per 100,000 population fell from 37 in 1948 and 35 in 1949 to 8 in 1958 and 8 in 1959. Diphtheria (586 cases and 21 deaths in the first year of the previous decade) disappeared—there were 7 cases in ten years, including none in the last four years. Whooping-cough declined from an average of 500 cases in 1950–1 to an average of 76 cases in 1956–9. Ophthalmia neonatorum virtually disappeared. So did scabies and ringworm. Poliomyelitis decreased from 36 cases in 1950 to 10 cases in 1958 and 1 in 1959." (*Health and Welfare*, issued by the Medical Officer of Health, Aberdeen, April, 1960.)