Histology: The brain, meninges, spleen and kidneys showed the fungus, which appeared as small spheres reproducing by budding. The lesions in the brain were meningeal and perivascular in the basal ganglia. The lesions in the brain and spleen had a minimal tissue reaction. In the liver and kidneys there were miliary collections of histiocytic cells containing the fungus. The firm nodule in the lung showed fibrosis, chronic inflammatory cells and two giant cells. There was no evidence of the fungus. It was not possible to be certain whether this was the primary focus of infection.

Discussion

Visceral infection by fungi may often be overlooked when there is no obvious skin lesion. In this patient the only possible portals of entry for the fungus could have been either the antrum, the X-ray of which showed an opacity, although there was no clinical evidence or any history of disease, or the lung, which showed evidence of previous disease.

The low antigenicity of most fungi does not lead to an acute inflammatory reaction; even a tissue reaction is slow to develop. When this occurs it is of a slowly developing granulomatous nature with the formation of a foreign-body type of giant cells as the fungus is treated as a foreign body. The presence of cystic spaces in the region of the basal ganglia and the gelatinous exudate of the meninges without acute meningeal inflammation show these aspects of the pathological process. The increase of

lymphocytes and the reduction of the chlorides and sugar of the CSF suggested tuberculous meningitis. But the lack of response to streptomycin and the slight alteration of the CSF chlorides and sugar on repeated lumbar puncture offered a clue to the probable cause of the meningitis.

Skin tests, complement fixation and precipitin tests were not done.

Treatment with the specific antibiotic amphotericin B was not possible as the patient succumbed before the drug was obtained from the United States.

The increasing incidence of fungal disease associated with the widespread use of antibiotics may tend to make cryptococcosis more common. The possibility of remission and arrest of the disease with amphotericin B makes it imperative that this disease be kept in mind and looked for before the patient is too ill.

Summary

A case of disseminated cryptococcosis with meningo-encephalitis is described.

Widespread lesions were revealed only at post-mortem.

A short description of the lesions in the brain and viscera is given.

The association of cryptococcosis with reticulo-endothelial disease is mentioned.

The importance of early investigation and treatment is stressed.

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BRONCHIAL ADENOMA WITH THE CARCINOID SYNDROME PRESENTING WITH UNUSUAL SKIN CHANGES

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THE term 'carcinoid' was first introduced by Oberndorfer in 1907 to distinguish certain atypical carcinomas of the bowel from ordinary adenocarcinomas. He gave a good histological description of the tumour and the chromaffin cells of which it was composed and thought it was benign. Carcinoid tumours are found most frequently in the gastrointestinal tract, with an estimated 60% to 90% of them in the appendix. They probably form from 0.1% to 0.5% of all tumours found at post-mortem

and only a small proportion of them give rise to the carcinoid syndrome, which was first described by Thorson, Biorck and Waldenström in 1954.

The clinical and biochemical features of the carcinoid syndrome produced by functioning carcinoid tumours originating in the bronchi have been reported in the last few years; of the 21 patients described, 19 have been associated with a bronchial adenoma and two with an oat-cell carcinoma. The following is a report of a patient

with a bronchial adenoma and the carcinoid syndrome who presented initially with unusual skin manifestations.

History. E. A., a male aged 49, born in Spain, was working as a waiter. He was referred complaining of redness and flushing of the face which had been getting very much worse for nine months. He said that all his life he had a tendency to flush after taking alcohol, but this had become more pronounced recently. On direct questioning it was found that he had had diarrhoea for the past five months and had lost two stones in weight in a year. He was not short of breath and had never had asthma. There was no significant family or personal history. In 1959 he had had a right-sided pneumonectomy (Mr. C. Grimshaw) at Peppard Hospital for an adenoma of the right main bronchus, known to be present since 1955.

On examination his face was continuously suffused a dark red with no obvious telangiectasia. The skin of his forehead was thickened and thrown into folds: that of his nose and cheeks was thickened and granular (Fig. 1). His chin, upper lip and sides of his face were less affected. The skin surface was shiny and greasy, with the pilosebaceous orifices patulous and exuding an oily sebum. His scalp was also greasy. The whole appearance was one of early leontiasis faciei with a fronto-, rhino- and zygo-phyma. Flushing of the chest was frequently observed, but was not easily produced by alcohol or hot drinks. The signs in his chest were compatible with a previous pneumonectomy. The heart sounds were normal, there were no murmurs and his blood pressure was consistently normal. The liver edge was palpable two fingers breadth below the costal margin.

Investigation and progress. Chest X-ray showed no abnormality in the remaining lung field. Barium meal showed a rapid progress through the small bowel with no evidence of neoplasm. The barium enema was normal. The qualitative test for five hydroxyindoleacetic acid (5-HIAA) was strongly positive, and the quantitative test showed values varying from 21 to 160 mg./24 hours (normal 1.5-8 mg./24 hours). Following a loading dose of tryptophan (3 g.) his urinary 5-HIAA increased from 65 mg. in 24 hours to 105 mg. two days later and 196 mg. five days later. The skin biopsy was reported as 'a mass of sebaceous glandular material with a few foci of chronic inflammatory change' (F. Hampson). Other tests, including blood count, liver function tests, keto-steroids and stool culture were normal. The ECG was also normal.

At laparotomy (Mr. G. L. Bohn) multiple evenly distributed metastases were found throughout the liver, but despite a very careful examination no tumours were found in the gastro-intestinal tract. Liver biopsy showed features histologically similar to those of the bronchial tumour.

The patient was discharged home after the operation and for a time he was asymptomatic but later there was a return of the flushing. He was treated with l-methyl-D-lysergic acid butanolamide tartrate ('Deseril') and cyproheptadine hydrochloride ('Periactin'), which are said to be antagonists of 5-hydroxytryptamine, without any effect on the diarrhoea or the flushing. He became increasingly emaciated, and his skin more pigmented. He died within six months of the diagnosis being established, and there was no post-mortem examination.

Discussion

Tryptophan is the only essential amino-acid

containing an indole nucleus. Part is used in the production of body proteins, but from the present point of view the main interest lies in two other pathways, one resulting in the formation of nicotinamide and the other in the production of 5-hydroxytryptamine (5-HT or serotonin, Udenfriend, Clark and Titus, 1953 a and b). By far the most important site of storage and probably of production of 5-HT is in the gastro-intestinal mucosa (Erspamer, 1955). Normally only 1% of tryptophan is converted to 5-HT and this is eventually excreted in the urine as 5-hydroxyindoleacetic acid (5-HIAA). This reaction is catalysed by the enzyme monoamine oxidase which plays a fundamental role in the inactivation of 5-HT (Erspamer, 1955).

Carcinoid tumours are uncommon and generally associated with the gastro-intestinal tract. Their association with the carcinoid syndrome is even less common. Nineteen cases of this syndrome associated with metastasizing bronchial adenoma have been reported (Anlyan, Hargrove, Ruffin, Wallace, Weaver and Kirschner, 1960; Bernheimer, Ehringer, Heistracher, Kraupp, Lachnit, Obiditsch-Mayer and Wenzl, 1960) Dockerty, McGoon, Fontana and Scudamore, 1958; Escovitz and Reingold, 1961

Gramlich and Wiethoff, 1960; Gerok and Muller, 1960, 1961; Husselman and Wendt, 1961; Krickler, Lackner and Sealy, 1958; Luparello and McAllister, 1960; Mattingly, 1956; Sandler, Scheur and Watt, 1961; Schneekloth, McIsaac and Page, 1959; Stanford, Davis, Gunter and Hobart, 1958; Warner and Southren, two cases, 1958; Williams and Azzopardi, 1960). In Krickler's patient the diagnosis was later confirmed by autopsy as reported by Sandler. The patient reported by Joseph and Taylor (1960) had deposits in the bowel, but can probably be accepted, because of convincing autopsy evidence. The patients reported by Pollard, Grainger, Fleming and Meachim (1962) and Toomey and Felson (1960) had extensive metastases, including osteoblastic bone lesions. In 1958 Sauer, Dearing and Flock reported two cases of primary bronchial carcinoids without the carcinoid syndrome. Warner, Kirschner and Warner in 1961 reviewed the literature and described two more patients with a raised serum 5-HT and raised urinary 5-HIAA without discernible metastases and without the carcinoid syndrome. As far as could be ascertained, none of these four patients had metastases in the liver, which probably explains why symptoms were absent. Bronchial carcinoids contain fewer chromaffin cells (Williams and Azzopardi, 1960) and produce less 5-HT, which is partly inactivated by the monoamine oxidase abundant in the lungs (Waldenström and Ljungberg, 1955). Proof of absence of a primary bowel carcinoid was obtained by autopsy or laparotomy in all the 19 cases quoted.

Harrison, Montgomery, Ramsey, Robertson and Welbourne (1957) and Williams and Azzopardi (1960) described the syndrome with an oat-cell carcinoma of the bronchus. This association is at first sight difficult to explain, but, as Bignall (1961) comments, oat-cell carcinomas are essentially undifferentiated tumours and, although histologically different from adenomas and adenocarcinomas originating from mucous glands, some of them may nevertheless be derived from the same tissues. If this is correct, there should be no surprise that bronchial adenomas and oat-cell carcinomas can both give rise to the carcinoid syndrome, presumably through the production of 5-HT.

The carcinoid syndrome, widely assumed to be due to the hypersecretion of 5-HT, presents with

flushing, diarrhoea and in some patients asthma and disease of the right side of the heart. It is generally associated with extensive liver deposits draining 5-HT into the systemic circulation. It is doubtful if 5-HT alone is responsible for producing the flushing (Robertson, Peart and Andrews, 1962). Adrenalin and noradrenaline may have a similar effect on some patients and alcohol, fat, cheese and tea have also been described as trigger agents.

Skin changes (Kierlander, Sauer and Dearing, 1958) may be marked or slight and consist of the paroxysmal transient flushing, generally of the face and neck, which may go on to erythematous or cyanotic patches due to the dilatation of the veins and capillaries, telangiectasia, oedema and chronic inflammation. 5-HT appears to be a factor in producing connective-tissue change and may produce sclerosis and atrophy of the skin simulating scleroderma (Bean, Olch and Weinberg, 1955; Zarafonetis and Kalas, 1960). At first there is erythema, and oedema which progresses to thickening, tightness, pigmentation and scleroderma-like change. Cutaneous metastases are rare, but have been reported. Pellagra-like skin lesions may be present (Thorson and others, 1954; Waldenström and Ljungberg, 1955), both because the diarrhoea gives rise to a vitamin deficiency and because some 60% of the ingested tryptophan is converted to 5-HT by the tumour. Characteristic features, such as redness, scaliness, pigmentation of the exposed areas, glossitis and angular stomatitis, may be accompanied by the mental changes of pellagra.

Constant flushing in this patient was associated with the appearance of a leonine facies with a phyma-rosacea, strikingly similar to the photograph of Mattingly's patient reproduced by Weiss and Ingram (1961). Rowell and Summerscales (1961) examined the urine of 21 patients with rosacea for 5-HT with negative results.

Summary

A patient with the carcinoid syndrome produced by a primary bronchial adenoma with liver metastases is described. He was initially referred to a dermatology department with flushing of the face giving rise to a phyma-rosacea. Details of 21 other patients have been collected from the literature and briefly reviewed.

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ERRATUM

'The Present Position in Coeliac Disease', A. V. Neale, POSTGRADUATE MEDICAL JOURNAL, May 1963, page 255, Fig. 1: Between GLUTEN and GUF ultracentrifuge should read ultrafiltration
Between DIALYSABLE FRACTION III and FRACTION IIIF ultracentrifuge should read ultrafiltration