Progress report

Mycoses of the alimentary tract

Fungi seem to be increasing in importance as the causal agents of disease in man, especially as secondary invaders in already debilitated individuals. Whether this increase is related to modern forms of treatment or whether it is due to our increased awareness of their existence and improved diagnostic procedures is unknown, although evidence is accumulating to suggest that modern therapy, especially for diseases of the reticuloendothelial system, is a contributory factor\textsuperscript{1,2,3}. At present evidence of systemic mycotic infection is uncovered in about 1 to 2\% of routine necropsies, a figure which rises to around 20\% if selected groups, such as those with leukaemia and lymphomas, are taken into account.\textsuperscript{3} One of the commoner sites of fungal invasion is the alimentary tract, and the object of this paper is to review certain aspects of such infections.

\textbf{DISEASES ORIGINATING IN YEASTS}

At least 13 genera, comprising over 100 identified species of yeasts, have been recovered from the gut of mammals. However, only a limited number of these have been incriminated as the cause of disease.

\textbf{CANDIDOSIS} While most of the available information on mammalian candidosis centres around man, and \textit{Candida albicans},\textsuperscript{4} Hurley\textsuperscript{a} has clearly demonstrated the pathogenic ability of three species of \textit{Candida} other than \textit{C. albicans} (\textit{C. stellatoidea}, \textit{C. tropicalis}, \textit{C. pseudotropicalis}) and has shown that each of the seven species (\textit{C. albicans}, \textit{C. tropicalis}, \textit{C. stellatoidea}, \textit{C. pseudotropicalis}, \textit{C. krusei}, \textit{C. guillermondii}, \textit{C. parapsilosis}) regularly isolated from the human host has been the aetiological agent of superficial and/or systemic candidosis. There is also evidence of the pathogenicity (at least to mice and rabbits) of \textit{C. viswanathii}.

The commonest clinical manifestation of \textit{C. albicans} infection is oral thrush—a disease universally recognized as common in infants and debilitated adults. In the typical mild case the disease first appears in the form of small white patches on the lining of the gums, the sides of the tongue, the buccal mucosa, and the mucosa of the throat. Lesions usually become confluent and form pearly-white raised patches which resemble curds of milk in appearance. After they are removed a raw surface is left. The lesions are usually painless with no swelling and heal rapidly within a few days of starting treatment.

Occasionally the disease may be more serious with erosion and ulceration of the oral mucosa and necrosis and granuloma formation. The various human clinical types have been reviewed by Lehner\textsuperscript{8} and Cawson\textsuperscript{7}. Of these, Candida leukoplakia is of particular interest. It seems clear that those chronic leukoplakia lesions, from which \textit{C. albicans} can regularly be recovered, have a specific histology and that abundant fungal elements can be demonstrated
in tissues. In the majority of patients there is, in addition, a significant rise in specific antibody titre, both in serum and in saliva. Treatment of this chronic infection involves the long-term application of antifungal drugs such as nystatin, and is, unfortunately, not always completely successful.\(^8\) It is possible that Candida leukoplakia may progress to malignant change, eg, squamous cell carcinoma.\(^9\)

Other diseases of the oral cavity in which yeasts appear to be of primary importance are angular cheilitis and denture stomatitis. In fact, Cawson\(^7\) has found that 80% of patients presenting with angular cheilitis were suffering from denture stomatitis, a form of candidosis in which the yeast proliferates in the space between the upper denture and the palate. Treatment of the stomatitis resulted in spontaneous cure of the mucocutaneous lesions.

The incidence of human alimentary tract candidosis (other than oral) as distinct from the isolation of \textit{C. albicans} from the gut is difficult to assess. It seems likely that it is rare, although it may be more common than might be expected from the infrequency of reported cases\(^10, 4\). Oesophageal candidiasis has been described on numerous occasions, usually in association with various systemic disorders and their treatment. The main symptoms include difficult and painful swallowing often associated with persistent retrosternal pain. Radiological features—a ragged and irregular outline—have been described\(^4, 11\). Candidosis has also been observed in the stomach and intestines\(^4, 12, 13\) and, except in early infancy, is probably always secondary to some gross constitutional disturbance. It is frequently accompanied by oral thrush or non-specific ulceration of the mouth. Invasion of the gastrointestinal mucosa is frequently followed by septicaemic candidosis which is disseminated to remote viscera.

Factors which favour the establishment of candidosis have been listed by Winner\(^14\). As far as the gut is concerned, the most important of these is prolonged antibiotic therapy\(^15, 16, 17, 18, 19, 20\). While candidosis has frequently been associated with malignant neoplastic and blood diseases\(^21, 12\), it is probable that this association arises from the use of therapeutic agents during the course of the disease\(^3\). Neutropenia appears to herald the onset of infection\(^11\). The presence of yeasts in the alimentary tract of neonatal infants is invariably followed by disease while alteration in salivary flow and mouth flora may also predispose to oral candidosis\(^22\).

Wilson and Plunkett\(^23\) believe that \textit{C. albicans} has a greater ability to diagnose the prediabetic state than physicians aided by modern laboratory tests. Their statement that ‘as soon as candidiasis is diagnosed or even suspected, the search for another disease should be the clinician’s first obligation’ would seem to be a useful rule.

While the diagnosis of oral candidosis can be made by the demonstration of hyphal forms of the yeast in smears from the lesion, gastrointestinal infections present more of a diagnostic problem. Mycelium may be present in the faeces, indicating possible mucosal invasion by the yeast\(^ 24\) while serological tests appear to be of some value\(^25, 26, 27\).

**OTHER YEAST DISEASES** Accounts of diseases said to be caused by other yeasts, such as species of \textit{Geotrichum}, \textit{Rhodotorula}, and \textit{Torulopsis glabrata}, are comparatively frequent in the literature, but in most cases convincing proof of the pathogenicity of the organisms is lacking.
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Geotrichosis of the bowel is a rare but recognized disease\(^{28}\), and cryptococcosis, usually regarded as a respiratory disease, or one of the central nervous system has been recorded in the alimentary tract\(^{29,30}\).

**DISEASES OF MYCELIAL FUNGAL ORIGIN**

Some idea of the range of filamentous fungi which can occur as transients in the gut has been given by Davies and Lesse\(^{31}\). However, only a very limited number of these have been found associated with lesions.

**MUCORMYCOSIS** Mucormycosis (phycomycosis) is an opportunist mycotic infection caused by fungi of the order Mucorales. It occurs in the presence of lowered host resistance and may affect any organ of the body. Fungi which have been incriminated are *Rhizopus arrhizus*, *R. oryzae*, *R. stolonifer* (syn *R. nigricans*), *R. microsporus*, *R. rhizopodiformis* (?R. cohnii), *Mucor ramosissimus*, and *Cunninghamamella elegans*.

Areas of the alimentary tract which have been found affected include the mouth, oesophagus, stomach, and intestines, the stomach and colon being the areas most commonly involved. Lesions vary from discrete superficial erosions to large, purplish, necrotic ulcers with diffuse areas of haemorrhage and necrosis involving all layers of the gut wall\(^{32,33,34,35}\). Widespread dissemination of the fungus from the primary gastric lesion is not common, which is rather surprising in view of the remarkable predilection of the organisms for growth within blood vessels. It may be that in most cases infection was acquired shortly before death giving the fungus little time to spread.

Unfortunately, little information is available on the symptoms of gastric mucormycosis as most cases were associated with some other more obvious disease and were only diagnosed at necropsy. Sex and race appear to have little influence on the incidence of infection while immaturity appears to be important.

Lesions in the oral cavity are secondary to cerebral or sinus infection. The lesions—ulceration and necrosis of the left side of the hard palate—apparently result from thrombosis of the greater palatine artery. All cases were in diabetics, 89% of whom were females.

Predisposing factors are apparently essential for the development of mucormycosis. Diseases with which infection is frequently associated are diabetes mellitus; leukaemia, lymphomas, and other malignant neoplasms; chronic debilitating renal and hepatic disease; malnutrition and diarrhoea\(^{32,36}\). Modern therapy for these diseases, with its prolongation of life, suppressive effect on protective mechanisms, cellular damage, and ecological disturbance of the gut microflora also appears important\(^{1,3}\). One feature common to most of the predisposing conditions is local damage to tissue and devitalization.

In the absence of suitable diagnostic tests (other than direct smears and culture from oral lesions), the clinician's best aid in the recognition of mucormycosis is the knowledge that such infections do not respond to antibacterial therapy and are frequently (possibly always) associated with well defined predisposing factors.

**ENTOMOPHTHOROMYCOSIS** Entomophthoromycosis is the name created by Clark\(^{37}\) to describe infections caused by fungi belonging to the order Ento-
mophthorales. Both mucormycosis and entomophthoromycosis are included under the term phycomycosis. Although entomophthoromycosis is primarily a disease of the subcutaneous tissues, deeper structures may be involved. Histological evidence of involvement of the large intestine and the jejunum has been found in two fatal cases. Both progressed from subcutaneous lesions.37

**HISTOPLASMA** Lesions in the mucosae of the oral cavity, larynx, stomach, and intestines are not uncommon in both acute and chronic disseminated histoplasmosis, particularly in adult males.38,39

In the oral cavity, the tongue seems to be the site of predilection while multiple foci—involving the lips, bucal mucosa, palate, and oesophagus are common. The lesions, small plaques or nodules which undergo central necrosis to form indurated ulcers, may in advanced cases result in marked tissue destruction and bone erosion. Their microscopic appearance varies considerably and appears to depend on the resistance of the host. As a rule, diagnosis of oral infection by serological or radiological tests is unreliable.

Involvement of the gastrointestinal tract as part of generalized fatal disease is common. Nodular or ulcerative lesions have been found in the stomach, small intestine (particularly the ileum), large intestine and rectum, and may result in perforations. Abdominal pain and diarrhoea have been attributed to colonic infection with *Histoplasma capsulatum* var. *duboisii* (as *H. duboisii*).40

Evidence41 to incriminate histoplasmosis in appendicitis and mesenteric adenitis is not convincing and it appears that intracellular elements interpreted as yeast cells of *H. capsulatum* were in fact only cellular remnants. As a number of widely diverse fungi—*Penicillium marneffii, Paecilomyces viridis, Torulopsis glabrata, Geotrichum candidum*—are capable of producing intracellular yeast-like cells similar to those of *H. capsulatum*42, the histopathological diagnosis of histoplasmosis should be confirmed by culture of the fungus.

**OTHER MYCELIAL FUNGAL DISEASES** Aspergillosis is a rare disease of the alimentary tract although *Aspergillus fumigatus* may colonize ulcerations of the stomach or duodenum resulting from other causes or infect the gastrointestinal tract as part of the generalized disseminated process.43

Lesions due to *Paracoccidioides brasiliensis* have been recorded in the oral cavity, lips, small intestine, particularly the ileum, and colon.2 Bogliolo44, in describing two cases of paracoccidioidomycosis (South American blastomycosis), postulated that the causative agent gained ingress along the teeth or through the periodontal tissues. Other workers have since suggested that the periodontal membranes, gums, and intestinal mucosa are of importance in the pathogenesis of paracoccidioidomycosis.45

North American blastomycosis (*Blastomyces dermatitidis*) is a disease which on rare occasions infects the tongue or oral mucosa.46

**SUMMARY**

Of the mycoses which have been encountered in the alimentary tract, candidosis and mucormycosis are of most significance and interest because
of their association with various predisposing factors. Invasions by the fungi responsible for these diseases appear to be due in part to impaired immunological states (spontaneous or induced by therapy) and agranulocytosis, local tissue damage and devitalization, and alteration in the ecological balance of the gut microbial flora.

Involvement of the alimentary tract is common in both acute and chronic disseminated histoplasmosis while oral and intestinal lesions appear to be important in the pathogenesis of paracoccidioidomycosis. Oral lesions have been recorded in North American blastomycosis and intestinal lesions in entomophthoromycosis. Other minor fungal diseases which have been found in the gastrointestinal tract, usually in association with some other disease, are aspergillosis, geotrichosis, and cryptococcosis.

Presently available antifungal agents and their biological activities have been listed by Drouhet, the most suitable of which are nystatin and amphotericin B. Nystatin is remarkably non-toxic (due to poor absorption through the gastrointestinal tract) and is the antibiotic of choice for candidosis of the alimentary tract. Amphotericin B is the first and only commercially available antifungal agent with activity against all the systemic mycoses. Side effects encountered with its use (nausea, vomiting, anorexia, chills, fever, headache) may be reduced by the use of corticosteroids and chlorpromazine.

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Gut 1969 10: 1035-1040
doi: 10.1136/gut.10.12.1035

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