INTRODUCTION
Candidosis is a disease caused both in man and animals by the mycelial yeast of the genus *Candida* especially *Candida albicans*. Candidosis has also been mentioned in literature as candidiasis, candidomycosis, moniliasis etc. Candidosis varies from an acute manifestation with eventual death to a mild chronic infection.

*Candida* species usually attack the superficial keratinized or mucosal parts of the body. At times, especially when the body defences are low, the viscera (especially the kidney) and circulatory fluids of the body are invaded by these fungi.

**HISTORY OF THE DISEASE**

In 1839 Langenbeck showed that thrush was caused by *C. albicans*. Thrush occurs in the mucous membrane of the mouth as large whitish plaques. There is pain and tenderness on deglutition. Children are more prone to this disease. Gruby in 1842, published a detail description of this disease.

Baum in 1960, isolated pathogenic *Candida* species from the oral cavities of man where they existed as harmless
commensals. These organisms can be isolated as saprophytes from various sites of healthy man or animals.

Van Uden (1960), isolated Candida species in horses, swine, sheep, goats, African bush pigs, African wart hogs, baboons and African pred crows. 38 per cent of the organisms isolated from the normal gastrointestinal tracts of these animals belonged to the Candida species. Carter et al., (1959), found 39% of the normal vaginal flora to be of this group. Recio and De Leon (1957), found Candida species in 46 per cent of the cultures from the perianal skin but they are rarely isolated from the exposed skin surfaces.

Mackenzie (1961), has isolated various Candida species from human urine, sputum, stool, throat, vagina and other sources.

PREDISPOSING CAUSES OF THE DISEASE

Various factors are responsible for the conversion of Candida species from harmless commensals or saprophytes to fully pathogenic forms. The most important factor being the host's innate immune defence mechanism. The host's immune responses are dependant on (a) hormonal disturbances, (b) certain idiopathic conditions, (c) pre-eminently receptive status, (d) debility due to other infectious diseases, (e) drug therapy, (f) accidental introduction of Candida
through faulty surgery and faulty transfusion of blood, glucose, saline or plasma.

ANTIBIOTICS & CANDIDOSIS

With the advent of the antibiotic era a gross increase in the incidence of candidosis was noted. The placement of antibiotics and steroids in the therapeutic firmament has induced subtle changes in the organisms or in the host whereby harmless commensals attain pathogenic proportions.

Downing and Conant (1945), in a comprehensive review of mycotic infections in the pre-antibiotic era found a negligible incidence of C. albicans.

Wessler and Brown (1945), attributed systemic moniliasis to prolonged sulphonamide and penicillin therapy.

Foley and Winter (1949), showed that penicillin treated chick embryos showed an increased mortality to C. albicans infection. As early as after five days of antibiotic therapy, an increase in the number of candidal strains isolated from the gastro-intestinal tract, was noticed (McGovern et al., 1953; McVay and Sprunt, 1951; Sharp, 1954).

Disseminated candidosis with high patient mortality is also attributable to antibiotics (Brown et al., 1953, Gausewitz et al., 1951; Kunstadter et al., 1952). Louria et al.,
(1960), and Levy and Cohen (1955), have found steroid therapy to increase the incidence of candidosis.

Seligman (1952, 1953), demonstrated that both chloroxytetracycline and cortisone when given to mice before intraperitoneal challenge with sublethal dose of \( C. albicans \) caused a substantial increase in the mortality of mice.

**IMMUNOSUPPRESSANTS AND CANDIDOSIS**

Immunosuppressants therapy of Cancer has alarmingly increased the incidence of candidosis (Torack, 1957; Baker, 1962). Hutter and Collins (1962), found 56% candidosis in 202 patients with neoplastic disease and 61 per cent of candidosis had Leukaemia-Lymphoma group of Cancer.

Baker (1962), showed that the advent of methotrexate, 6-mercaptopurine, vincristine etc. as antileukaemic drugs has raised the mortality of leukaemic patients due to gastro-intestinal candidosis. Ulceronecrotic gastro-intestinal lesions due to the damage to the reticuloendothelial system promotes the dissemination of \( Candida \) to the point of death of the patient within 3-4 days.

Mukherji and Basu Mallick (1972), showed that mice treated with another immunosuppressant cyclophosphamide had a more severe and disseminated form of candidosis than normal mice.
Mass antifertility programme and the usage of steroidal oral contraceptives have contributed towards a high incidence of candidosis (Diddle et al., 1969; Porter and Lyle, 1966 and Walsh et al., 1968).

**Sites of predilection of Candida albicans**

As a commensal *C. albicans* is found in the mouth, intestines and vagina. It is also associated with a variety of cutaneous and mucosal surface lesions. Deep seated infections are found in organs like the kidney, heart, liver, central nervous system, lungs, spleen, deeper tissues of the digestive tract and less frequently the pancreas and thyroid.

**DRUGS USED IN CANDIDOSIS**

Polyene antibiotics (Ascocin, Amphotericin B, Pimaricin, Candidin, Trichomycin, Hamycin, Candicidin etc.) are the antibiotics of choice for the treatment of superficial candidosis like thrush. These antibiotics are ineffective against deep seated candidosis (abscesses of the viscera especially the kidney). This is due to the fact that low blood concentrations are produced when given systematically (Drouhet, 1968).

Polyene antibiotics have low oral but high intravenous toxicity. Amphotericin B is the most effective
antibiotic for the treatment of systemic candidosis. High dosages, over a long period of time, (Sarosi et al., 1969), with incidental toxicity shows how very difficult it is to treat systemic candidosis.

Amphotericin B displays cytotoxicity on the cells of monkey kidney epithelium, Hela, KB, human intestines etc. Orally mice and rats tolerate 8,000 mg./kg. and 1000 mg./kg. of amphotericin B (Littman et al., 1958). Bartner et al., (1958), estimated in mice the lowest lethal dose ($LD_2$) to be 2.2 mg./kg. and the average lethal dose ($LD_{50}$) to be 4.5 mg./kg. when amphotericin B is given intravenously.

Oral daily dose of 16 gm. of amphotericin B is well tolerated and free from side effects (Newcomer et al., 1959), Harrell and Becobo, 1960). Intravenous administration in man gives rise to pyrexia, chills, nausea, headache, general malaise and elevation of blood urea nitrogen. Renal effects are serious enough to cause either reduction of dose temporary or complete withdrawal of the drug (Utz., 1966).

Different regimens of amphotericin B are sometimes used in view of the seriousness of systemic disseminated candidosis and the toxic potentiality of amphotericin B (Bindschadler, and Benett, 1969; Drutz et al., 1968. None of these regimens are therapeutically fully acceptable as the effectivity of amphotericin B is not increased neither
the toxicity is lowered.

The tetraene nystatin is non-toxic at an oral dosage of 4-8 gm. (8-16 x 10^6 units). Nystatin lacks toxicity due to its poor absorption from the gut. It is, therefore, of no value in the treatment of systemic mycosis.

Hamycin is a heptaene antibiotic described by Thirumalachar et al., (1961). Opinions differ regarding the gastro-intestinal absorption of hamycin. The oral toxicities and biological activities of different batches of hamycin vary considerably. Hamycin fails to act against systemic candidosis due to its poor absorption from the alimentary canal.

Candididin, ascospin and trichomycin are toxic by the oral route. They are not absorbed from the intestinal tract, and hence per os they are ineffective against systemic candidosis. Pimaricin is also a highly toxic drug.

5-fluorocytosine and clotrimazole are newer drugs found effective in animal infections. They are being tried in severe candidosis in humans under controlled hospitalized conditions.

Procknow (1962), states that the present therapeut- tic armamentarium including antifungal antibiotics can not effectively cure disseminated forms of candidosis.

Drouhet (1968), opines "After the discovery of antibacterial antibiotics and the associated increased
incidence of fungal complications such as candida infections, the need to control the mycoses became imperative and stimulated a vigorous search for antifungal antibiotics. Nevertheless, most antifungal agents are effective only on the superficial mycoses. The deep mycoses, with their chronic and sometimes fatal courses, are even now the most difficult infections to control.

**Immunity in Candida infections**

Soluble proteins and certain polysaccharides of pathogenic micro-organisms (antigens) evoke an antigonistic response in the human or animal body. Antibodies are generated which in some cases are sufficient to ward off a second attack. This is the basis of immunity against disease. Artificially immunity can be built up by injecting killed or live attenuated micro-organisms or their products. These act as antigens and stimulate antibody production to establish a state of immunity.

It appears worthwhile to examine the role of immunity in the pathogenicity of *Candida* in general and to investigate the applicability of immunologic methods for the protection against moniliasis and for the treatment of disseminated forms of the disease.

A voluminous serologic literature dealing with
taxonomic considerations and diagnostic tests exist, but according to Kligman and De Lamater 1950, little experimental work has been devoted to the study of immunization against candidosis. The reasons may be that since natural immunity may not be clearly demonstrated following Candida infection, a development of an anticandida vaccine may not have been considered promising.

It appears worthwhile to discuss the immunological basis of resistance against this infection and examine some of the experimental evidences and observations already made on this subject. Literature survey did not reveal any report on the use of active or passive immunization in human candidosis. Hurd and Drake (1953), Winner (1956 and 1958), using the rabbit as a model, failed to demonstrate any immunity to C. albicans.

Mourad and Friedman (1961), Hanselever and Mitchell (1962a; 1962b; 1963a and 1963b), conclusively demonstrated immunity against C. albicans when mice were vaccinated with C. albicans, Salmonella enteridis or Salmonella typhosa lipopolysaccharide or complete Freund's adjuvant.

**OUR APPROACH**

Judging the gravity of systemic deep seated Candida infection in man and animals, it was considered
desirable to study this problem from two different angles. The first was the empirical chemotherapeutic approach by which several new synthetic compounds of different structure types and some antibiotics have been studied 'in vitro' and 'in vivo'. 'In vivo' experimental candidosis were produced in the mouse. Amphotericin B and nystatin were used as the standard reference drugs. One antibiotic and one synthetic compound were subjected for detailed study histopathologically and by means of viable counts.

The second was the immunological approach. Using the mouse model, the effect of specific and non-specific vaccination, have been studied. *Streptococcus faecalis*, a gram-positive bacteria, was found to protect mice against *C. albicans* challenge. *Streptococcus faecalis* have therefore been fractionated with a view to isolate and possibly identify the nature of the immunogenic material.

Whether chemotherapy or immunotherapy would provide the answer for deep seated systemic candidosis or not, is still debatable. It may be that both chemotherapy and immunotherapy have to be given simultaneously. It may also be possible that some brilliant synthesis may produce drugs which may augment impaired host resistance and thereby help in the problem of systemic candidosis.