INTRODUCTION

I. Candida albicans (Bulmer, 1969) :

- Colony morphology

Colonies on Sabouraud's glucose agar (S.G.A.) at 25°C appear creamy smooth and raised within 24-48 hours.

- Microscopic morphology

1. S.G.A. yeast cells are short ovoid (5 to 7 u) sometimes elongate.
2. On corn meal agar (C.M.) mycelium and pseudomyceluim formed, masses of blastoconidia at internodes terminal thick walled chlamydospores are formed by most strains.
3. All strains of Candida albicans produce germ tubes in serum after 2-3 hours incubation at 37°C.

- Fermentation

Glucose	+	Inulin	-
Sucrose	±	Raffinose	-
Maltose	+		
Galactose	+		
Lactose	-		

- Assimilation

Glucose	+	Lactose	-
Galactose	+	Raffinose	-
Sucrose	+	Starch	+
Maltose	+	Inulin	±

II- Candida tropicalis :

Hasenclever and Mitchell (1961) have reported that Candida tropicalis and Candida albicans group A were antigenically identical.

- Colony morphology

1. On S.G.A. : as Candida albicans.
2. On corn meal agar : there is short, much branched pseudohyphae. Some strains of Candida tropicalis produce chlamydospores especially on initial isolation. These differ from those of Candida albicans in that, they do not have a supporting cell.
3. Some strains of Candida tropicalis may produce germ tubes in serum when incubated at 37°C for 3 hours but the germ tube shows a narrowing or constriction at the emergence from the yeast cell. Such constrictions are not seen in germ tubes of Candida albicans.

- Fermentation

Glucose	AG +	(Acid and gas)
Galactose	AG +	
Sucrose	AG +	
Maltose	AG +	
Lactose	-	
Raffinose	-	
Inulin	-	

- Assimilation

Glucose	+	Galactose	+
Sucrose	+	Maltose	+
Starch	+	Lactose	-
Raffinose	-	Inulin	-

III- Candida stellatoidea (Bulmer, 1969) :

- Colonies on S.G.A. : as Candida albicans, but are slow growing and smaller in size.
- On C.M.A. : much branched pseudomycelium in tree like arrangement are composed mostly of short cells, irregular clusters of blastoconidia. Chlamydospores are rarely produced.
- Incubation in serum : it does not produce germ tubes.

- Fermentation

Glucose	AG +	Maltose	AG +
Sucrose	-	Lactose	-
Galactose	-	Raffinose	-
Inulin	-		

- Assimilation

Glucose	+	Maltose	+
Galactose	+	Sucrose	-
Lactose	-		
Inulin	-		

Most strains come from vaginal discharges Hasenclever and Mitchell (1961) have reported that Candida stellatoidea and Candida albicans group B were antigenically distinguishable.

IV- Candida pseudotropicalis (Bulmer, 1969) :

- Colony :
  - On S.G.A. as Candida albicans.
  - On C.M.A. pseudomycelium is abundant, the cells are very elongated and Blastoconidia are not present and if present, they are elongated.
  - No germ tube production.

- Fermentation

Glucose	+	Sucrose	+
Galactose	+	Lactose	+
Maltose	-	Raffinose	+
Inulin	+		

- Assimilation

Glucose	+	Sucrose	+
Galactose	+	Lactose	+
Maltose	-	Raffinose	+
Inulin	+		

V- Candida krusei (Bulmer, 1969) :

- Colony :
  - On S.G.A. : colonies are flat, dull and dry.

On C.M. no pseudomycelium, only branched chains of round cells.

- Fermentation :

Glucose + Trehalose +

- Assimilation :

Glucose only +

- Antigenic composition

The various species of Candida have been classified into six antigenic groups according to slide agglutination tests with monospecific absorbed rabbit sera (table A) (Abraham, 1982). Each of 22 species of Candida were grouped,according to their content of seven heat stable and three heat labile antigens. In this system of classification, both Candida stellatoidea and Candida tropicalis are closely related antigenically to Candida albicans. Although all Candida species share a common antigen, the antigenic structure of Candida pseudotropicalis, C.krusei, C.parapsilosis are distinctly different from C.allbicans. These antigenic relationships have been largely substantiated by means of immunoelectrophoresis of soluble yeast extracts (Biquet et al., 1965).

The important antigenic determinants in Candida species appear to be surface polysaccharides, such as mannas and glucans. Mannas form the outer layer and glucan the inner layer of the cell wall of C.albicans. The two sugars appear to occur naturally as complexes of polysaccharide protein, linked together by N-acetyl-glucosamine. The antigenic specificity of the mannas depends on the length of the polysaccharide side chains and the type of glycosidic linkages present in them the mannas are polymers of mannose, that is the main chain

or the backbone of Candida albicans. They are connected by alpha 1 to 6 linkages. Two serotypes of Candida albicans have been described, which antigenic distinction may depend on the number and position of the linkages (Abraham et al., 1982). These two serotypes are Candida albicans A and C. albicans B. C. albicans group B was isolated from more clinical specimens than Candida albicans group A. (Hasenclever and William, 1961). Group A seems to be almost antigenically identical to Candida tropicalis and group B is antigenically similar to Candida stellatoidea.

Table (A): Antigenic grouping of Candida species of medical importance (Abrham et al., 1982).

Group	Species	Thermostable antigens	Thermolabile antigens
I	C.albicans	1,2,3,4,5,6,7	
	C.tropicalis	1,2,3,4,5,6	
II	C.stellatoidea	1,8,10	a
	C.pseudo-tropicalis	1,2,3,4,5,10	
III	C.krusei	1,2,5,11	b
IV	C.parapsilosis	1,2,3,5,13,14,15	c

Immunology

The host defences against candidiasis are both specific and non specific, cellular and humoral (Wolfgang, 1980).

Cell mediated immunity is thought to be more important than humoral immunity in resistance to candida infections. There is more evidence that candidiasis occurs because the T cell can not recognize the antigen or produce migration inhibition factor. There is also suggestive evidnece that macrophage chemotaxis is depressed (Abraham et al., 1982).

Cellular host defences against candida involve neutrophils, which kill 30-40% of the ingested yeasts and the effector functions of macrophages (Wolfgang,1980).

The natural immunity of healthy persons to candida infection is probably generated early in life,when the alimentary tract becomes colonised with C.albicans. The surface glycoproteins (manna proteins and glucoproteins) are thought to stimulate both humoral and cellular immunity. Thus normal people develop antibodies and delayed hypersensitivity to candida culture filtrates, which contain glycoprotein and polysaccharide antigens (Abraham, 1982).

The factors responsible for this natural resistance appear to be many and varied. Serum components, such as

opsonins, complement, transferrin may inhibit either directly or indirectly the survival of candida. Specific antibodies to candida have a minimal direct effect, but they may :

- Inhibit the normal clumping of yeast by serum.
- Affect yeast morphogenesis, respiration or function.
- Mediate antibody dependent cellular cytotoxicity.

Serodiagnosis and serological identification

It was realized that patients with candidal infections as well as normal subjects,showed hypersensitivity to skin testing with candida antigen and that many people had agglutinins in their sera.There is an increasing evidence that the presence of immunodiffusion bands and perhaps complement fixation titres are of diagnostic values (Odds, 1979).

Merz et al., (1977) evaluated the relative sensitivity and specificity of several serological test, including : agar immunodiffusion (ID) whole cell agglutination, latex agglutination and counter immunoelectrophoresis. In laboratory, the ID and latex agglutination are best used.

Serological identification is feasible by fluorescent antibody techniques, and by slide or tube agglutination with species-specific (suitably absorbed) antisera.

Serological tests are positive only in disseminated candidiasis.

Pathology

Louria (1964) stated that the transformation of yeast cell to mycelium form, helped the organism to escape macrophage ingestion and it was necessary for invasion of tissue (Montes, 1968). Thus, the mycelial phase of candida was considered the pathogenic stage and the yeast stage, the saprophytic form. Recently, investigations revealed that the yeast stage is necessary for initiation of a lesion and that the mycelium is formed upon exposure to environmental factors. When yeast cells present in large numbers, they cause toxic and inflammatory reactions. The pathologic processes, evoked are diverse and vary from irritation and inflammation to chronic and acute suppuration or granulomatous response. Since C.albicans is an endogenous species, the disease represents an apportunistic infection (Rippon, 1982).

Once actual colonization has occured and invasion has begun, the proportion of mycelial elements increases. Thus predominance of yeast forms indicates recent lesion, whereas in old lesions mycelia are found.

Etiology, Ecology and Distribution

Although the etiologic agent Candida albicans is usually encountered in most of the clinical forms of candidiasis, in some of the less common clinical conditions, such as endocarditis, other species are more frequently

isolated. These other species represent normal flora of the cutaneous and mucocutaneous areas and are of very limited pathogenecity. All species may be involved in any form of candidiasis, but some are regularly encountered in one particular type. These include C.parapsilosis from paronychias, endocarditis and otitis externa, C.tropicalis from vaginitis, intestinal disease, bronchopulmonary and systemic infections and onychomycosis, C.stellatoidea from vaginitis, C.guillermondii from endocarditis, cutaneous candidiasis and onychomycosis, C.pseudotropicalis from vaginitis, C.glabrata from oesophageal and vaginal lesions; C.krusei very rarely from endocarditis and vaginitis (Rippon, 1982).

Candida albicans is a normal inhabitant of the alimentary tract and the mucocutaneous regions. It is regularly present in small numbers in the mouths of normal healthy adults. Poor oral hygiene or even small amounts of antibiotics promote an increase in the number of organisms, though usually without untoward results. It is well established that candidal vaginitis during pregnancy contributes to thrush of the newborn. A small but significant percentage of cases are due to cross contamination from other infants, mothers and personnel. C.albicans is frequently found on fingers, and these are the probable vectors for intrapersonal as well as person-to-person dissemination (Bulmer, 1969).

The incidence of C.albicans in the normal vagina of healthy, nonpregnant women is about 5% and can be as high as 30% in pregnant women or women on oral contraceptives. There is a distinct increase in clinical vaginitis in gravid women. Most studies indicate a rate of candidiasis of about 18% for nonpregnant women with vaginal discharge, but an average rate of 30% for gravid women and women on contraceptives (Hurley, 1973).

The normal alimentary tract has a small, but constant population of C.albicans. Under normal conditions, this is probably influenced by foods, since diet markedly affects the total number of organisms present. In the young, before a balanced flora is established, initial colonization of the intestine is frequently associated with clinical symptoms. Perianal colonization may also occur, followed by diaper rash. In the adult, two extrinsic factors alter the number of C.albicans in the intestine(Bulmer,1969). First, it has been established that other members of the intestinal flora exert a control on the population density of the yeasts. Studies have implicated a variety of antimicrobial factors, and probably no single mechanism is totally responsible. However, lactic acid appears to be quite inhibitory to C.albicans, and a correlation has been found between the numbers of lactobacilli and other lactic acid producing organisms present and the

number of yeasts. Secreted inhibitory factors, oxidation-reduction potentials and competition for available nutrients have also been implicated in yeast population control. It was observed quite early that a change in the intestinal flora following orally administered antibiotics, greatly influenced the number of C.albicans. The overgrowth of organisms may manifest itself only as an irritating pruritis and or progress to colonization of the intestinal tissue and eventual fatal systemic candidiasis (Timonen et al., 1966 and Bulmer, 1969).

The second factor, influencing the population of C.albicans is diet. A high fruit diet appears to favour a rapid increase in the number of intestinal yeasts and probably explains the former postulated association of candida and tropical sprue. In normal adults, who maintain this diet, there doesn't appear to be any symptomatology after acclimatization of the host to the presence of the organism (Bulmer, 1969).

The normal skin appears to have a resident yeast flora, but this does not include C.albicans (Wolfgang, 1980).

Whereas normal skin does not harbour a resident flora of C.albicans, almost any damage to skin or enviromental change leads to rapid colonisation. For this reason, candida is not infrequently isolated from a variety of dermatologic conditions. Most of the lesions are situated

in moister areas, such as the inflammatory folds, the perianal skin and other intertriginous regions. Fruit pickers, canners, dishwashers are particularly prone to candidal infections of the fingers, since constant contact with a moist environment leads to maceration of skin. Endocrine balance, the administration of steroids and other physiological factors influence the rapidity and extent of C.albicans colonization. Although this organism may not have initiated a particular lesion, once it is established, it contributes to the pathology of the disease (Bulmer, 1969).

Age and sex distribution as well as clinical manifestations of candidiasis are markedly affected by varying predisposing factors and the underlying disease of the patient. There are five general conditions, in which the normal equilibrium between candida and the host may be sufficiently upset to lead to a pathologic state (Hurley, 1969; Bulmer, 1969, and Rippon, 1982).

1. Extreme youth

During the normal process of establishing a resident flora, the restricting factors for candida may be absent, and a clinical condition is produced (thrush, diaper rash, etc.). In normal children this condition resolves rapidly, often without treatment.

2. Physiologic change

Pregnancy appears to affect the carbohydrate

content of the vagina and leads to an increase in the population of candida. This overgrowth may be sufficient to cause a clinically apparent vaginitis. The administration of steroids to males or females also leads to proliferation of candida. This would also include patients with endocrine dysfunctions, particularly diabetes. The normal flora carrier rate on the skin of diabetics is quite high, and the number of the organisms in the usual colonized areas (buccal mucosa, intestine, vagina) is also increased. All of these factors contribute to the commonness of opportunistic infections in diabetics.

3. Prolonged administration of antibiotics

Much evidence has accumulated, associating clinical disease with the use of antibacterial antibiotics. The most important effect is the elimination and alteration of the bacterial flora that holds the population of candida in check. Evidence also suggests that there is some effect of the antibiotic on the host tissue that predisposes it to invasion by the organism, and the antibiotic itself may stimulate the growth of the candida. The occurence of the current investigations tend to discount it.

4. General debility and the constitutionally inadequate patients

The list of disease syndromes, associated with candidiasis is long and varied. The extent and severity

of the disease usually correlates with the severity of the underlying illness. The term debility comprises such things as the slight avitaminosis of the aged, which leads to thrush, diabetes and its associated cutaneous candidiasis, candidal vegitations of diseased heart valves; and pulmonary or generalized systemic candidiasis,occurring as a sequela to chronic disease or as a terminal event in the various neoplasias. Debility may also be iatrogenic. Immunosuppresive agents, cytotoxins and other drugs abrogate the normal defenses of the host and predispose them to candidiasis or invasion by other opportunistic organisms. Constitutionally, inadequate patients include those,with various immune defects and defects,associated with abnormal leukocytic function.

5. Iatrogenic and barrier-break candidiasis

Can result from a wide variety of insults. In the first type colonization can occur in association with indwelling catheters, hyperalimentation,peritoneal dialysis and surgical procedures or simply through the injection of material into the skin, muscle or circulatory or central nervous system. Drug abusers often develop candida infections at the site of injection or on heart valves. Candida infections may also result from accidental barrier breaks such as trauma, burns or gun or knife wounds.

Factors predisposing to candida infection (Rippon, 1982)

I. Physiologic	: Pregnancy
	Old age
	Infancy
II. Traumatic	: Maceration
	Wounds
III. Hematologic	: Cellular immunodefficiency
	Aplastic anaemia
	Agranulocytosis
	Lymphoma
	Hodgkin's disease
	Leukemia
	Hypogammaglobulinaemia
IV. Endocrine	: Diabetes mellitus
	Hypoparathyroidism
	Addison's disease
V. Iatrogenic	: Immunosuppression
	Transplantation
	Post operative
	Steroid treatment
	Antibiotics
	Contraceptive pills
	Catheters
	Vaccination

VI. Miscellaneous : Malignancy
Malnutrition
Malabsorption
Heredity.

Prognosis :

As candidiasis is primarily an opportunistic infection, prognosis depends almost entirely on the type and severity of the predisposing conditions or diseases. Oral thrush in the newborn healthy child may clear unevenfully, but other forms of candida infection are much more difficult to treat and usually do not clear spontaneously. Control of cutaneous candidiasis in the diabetic depends on proper hygiene and regulation of the diabetes. In candidiasis, associated with macerating conditions, prolonged exposure to moisture, and so elimination of these factors will cause resolution of the disease even without treatment. Chronic disease in the constitutionally inadequate patient can be controlled with therapy but the condition will return with cessation of therapy. In advanced systemic diseases, candidiasis is usually a terminal event, which contributes to the ultimate demise of the patient (Bulmer, 1969).

Factors that favour the establishment of candida in the vagina

King et al., (1980) examined the in vitro adherence capabilities of seven Candida species, where adherence was evaluated by direct microscopic examination and by a quantitative radiometric adherence test. The result of both tests indicates that C.albicans adheres to vaginal and buccal epithelial cells to a significantly greater degree (P 0.01) than the other species tested. They found that C.tropicalis and C.stellatoidae show moderate adherence capabilities, while C.parapsilosis adhered only to a slight degree. Other species failed to interact with isolated mucosal cells. Their findings suggest that there is a relationship between the adherence capabilities of the Candida species and their abilities to colonize mucosal surface, since those species, which adhere are those which most frequently colonize mucosal surfaces. Adherence to epithelial cells is the initial step in the process, by which certain bacteria colonize mucosal surfaces (Gibbons and Van Houte, 1975,and Reed Williams, 1978). Such attachment enables the organisms to avoid elimination by the cleaning action of bathing mucosal secretions. In a similar fashion, the ability of C.albicans blastospores to adhere may explain the mucosal colonization properties exhibited by this organism

(King et al., 1980). Furthermore, variations in the adherence capabilities of Candida species might in part, explain why some was found to colonize these surfaces more frequently (King et al., 1980). Thus a relationship apparently exists between the relative ability of the Candida species to adhere and their ability to colonize and subsequently infect mucosal surfaces.

The nature of the factor (S),which mediates C.albicans attachment to epithelial cells remains undefined, but King et al., (1980) indicated that adherence is temperature dependant and can occur under both alkaline and acidic conditions. The latter observation is significant in that adherence was obtained at pH values consistent with the mucosal surfaces of the vaginal (pH 5.0) and oral cavities (pH 7.0)(Botella, Luisia, 1973). Other factor (S) as indicated by King et al., (1980), responsible for adhesion, appear to be present to a greater extent on the surface of stationary-phase blastospores than on cells in the logarithmic phase of growth. They had found that the source of the mucosal epithelial cells had a marked influence on adherence. Although they were of approximately the same size,vaginal epithelial cells tended to adhere more candida, than did the buccal cells. They also observed significant variations in adherence when vaginal epithelial cells were obtained from different donors. These differences may reflect the

relative susceptibilities of these individuals for candidal colonization. Moreover, they had shown that, quantitative adherence values may be influenced by the hormonal status of the individuals at the time, that the vaginal cells were collected. Hormone levels have been shown to influence the adhesion of group B streptococci to vaginal epithelial cells (Botta, 1979). Whether such a relationship exists for candidal adherence remains to be determined (King et al., 1980).

Role of candida in vaginitis

There are variations in the reported frequencies of symptoms due to candida infection (candidosis, or candidiasis). The most common figures state that 2/3-1/2 of the patients are symptomless (Hopsu-Havu et al.,1980). About one third to one half of these carrying candida infection are usually reported to suffer from vulvovaginal symptoms (Hopsu-Havu et al., 1980). Hopsu-Havu et al.,(1980) found that about two thirds of the women, with yeasts,were considered symptomatic cases.

Diabetes, antibiotic therapy,oral contraceptives, and pregnancy may predispose to vaginal candidiasis. The disease is characterized by the presence of a thick yellow, milky discharge, and patches of grey white pseudomembranes (curdlike patches) are seen on the vaginal mucosa. The lesions vary from a slight ectzematoid reaction,with minimal erythema,to a severe disease process

with pustules, excoriations and ulcers. The whole area is greatly inflamed, and pruritis is usually intense. Papular and rarely ulcerative lesions may occur, and the condition may extend to involve the perineum, the vulva and the entire ingiunal area. Candida infections have long been associated with pregnancy. The rate is highest during the third trimester, when vaginal pH is lowest. In nonpregnant women, the discomfort of vulvovaginitis may be particularly intense just prior to menstruation. Pruritis and pain in the introitus and labia minor can be aggravated by urination, sexual intercourse, or gynaecological examination. Many patients experience symptoms after a warm bath or while in bed. The condition can be mimicked or may coexist with trichomonas vaginitis. In the latter disease, low level pruritis is constant and the curdlike patches are lacking (Rippon, 1982). Bacterial vaginitis such as corynebacterium vaginale also mimic candida disease.

Infection and reinfection occur by way of contamination from the digestive tract (Rippon, 1982). Candida albicans accounts for most cases of vaginitis with some cases being caused by C.glabrata, C.tropicalis, C.stellatoidea and other species.

Vaginal candidiasis and contraceptive methods

It has been reported that patients given oral

contraceptive medications, may have symptomatic vulvovaginal candidiasis more commonly than those not given these drugs (Editorial, 1967). Candida albicans increased in pill users till a period of four years then it decreased with the duration of pill intake but was still significantly higher than the control group. In intrauterine cervical devices, it increased with the increased duration of the device (El-Ghazzawi et al., 1979). Gardner(1967) had reported that women, given oral contraceptive medications had a five fold increase in the incidence of vulvovaginal candidiasis as contrasted to a similar group of women not given one of the pills.

Susceptibility to mycosis is enhanced with the increase of glucose level in the vaginal secretions and desquamation of glycogen rich epithelial cells due to the same reason (Nabaum, 1970 and Robert, 1972).

Many authors showed controversial results, regarding the incidence of vaginal moniliasis in pill users (Morris et al., 1967 and Spellacy et al., 1971). However it was increased (36.7%) in the result of Fares et al., (1979).

Wynn and Doar(1966) discovered that the contraceptive pills impaired glucose tolerance. They found a significant increase in the serum triglycerides of those women taking one of the contraceptive pills. Walsh et al., (1968) implicated the oral contraceptive agents as effecting a higher average blood glucose tolerance concentration

than normal. These drugs alter the vaginal chemistry and predispose to growth of the candida organisms. Kalund et al., (1970) and Spellacy et al., (1971) found that the concentration of insulin and glucose in plasma influences the vaginal epithelium, and acidity, causing increased incidence of acidity, causing increased incidence of Candida albicans in pill users in the cases studied by Fares et al., (1979). Also they found that, the incidence of moniliasis increases with the increase in duration of pill intake.

Fares et al., (1979) found that 29% of positive cases of Candida albicans did not complain of cheesy discharge, itching, burning sensation or dyspareunia.

Sylvia et al., (1953), and Ris and Dodge (1973) stated that patients with yeast infection alone usually do not complain of excessive discharge. This may prevent a pill user from seaking medical care.

Timonen et al., (1966) and Valerie et al., (1972) found that the presence of Candida albicans and its pseudomycelia in smears of vaginal secretions does not rule its presence as shown later by culture (20% by smear and 36.7% by culture).

Proliferation of the fungus depends on an underlying factor, such as allergy, lowered resistance, continuous inoculation trauma, diabetes mellitus and/or

antibiotics. This may change a carrier state to an acute pathological process. Taking into consideration that, all the above mentioned factors were excluded in the choice of the sample, this slows clearly the effect of oral contraceptives of the combination type and the effect of bad hygien (Walsh et al., 1968 and Fares,1975) on the incidence of moniliasis.

Candida albicans was always accompanied by pathogenic and non pathogenic organisms e.g. Staph. aureus and Lactobacillus respectively (Walsh et al., 1966).

Candidal vulvovaginitis in diabetes

Diabetics are more susceptible to vulvovaginal candidiasis. Candidal vulvovaginitis preceeds by several years the open manifestations of diabetics (Wolfgang,1980). It is common to order a blood glucose test for patients with persistent or repetitive candidiasis, diabetes is frequently discovered in this manner. Vulvovaginitis increases in diabetics because of glycosuria, increased glycogen in vaginal mucosa, the pH is highly acidic (3.5-6.8)and continued excess moisture (Toppozada,1978).

Treatment of candidal vulvovaginitis

There are many preparations available for the treatment of candidal vulvovaginitis and they come in a variety of vehicles such as creams, lotions,pessaries

and foaming pessaries. The form or vehicle appears to make little difference as far as efficacy is concerned and is a matter of personal preference. Two major groups of pharmaceuticals now in vogue are the imidazoles and the polyenes. Four polyenes-pimaricin, candicidin, amphotericin B, and nystatin have been used topically, nystatin being the most popular. Most recent studies, however, indicate the imidazoles give higher cure rates than the polyenes. Clotrimazole, miconazole, ketoconazole, and econazole have all had clinical trials. At present clotrimazole topically for two weeks appears to be the favourate. Resistant infections and reinfections are common (Rippon, 1982).