SUPPLEMENT ARTICLE

Candida Urinary Tract Infection: Pathogenesis

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Candida **species are unusual causes of urinary tract infection (UTI) in healthy individuals, but common in the hospital setting or among patients with predisposing diseases and structural abnormalities of the kidney and collecting system. The urinary tract may be invaded in either an antegrade fashion from the bloodstream or retrograde via the urethra and bladder.** ***Candida*** **species employ a repertoire of virulence factors, including phenotypic switching, dimorphism, galvano - and thigmotropism, and hydrolytic enzymes, to colonize and then invade the urinary tract. Antegrade infection occurs primarily among patients predisposed to candidemia. The process of adherence to and invasion of the glomerulus, renal blood vessels, and renal tubules by** ***Candida*** **species was elegantly described in early histopathologic studies. Armed with modern molecular biologic techniques, the various virulence factors involved in bloodborne infection of the kidney are gradually being elucidated. Disturbances of urine flow, whether congenital or acquired, instrumentation of the urinary tract, diabetes mellitus, antimicrobial therapy, and immunosuppression underlie most instances of retrograde** ***Candida*** **UTI. In addition, bacterial UTIs caused by Enterobacteriaceae may facilitate the initial step in the process. Ascending infections generally do not result in candidemia in the absence of obstruction.**

In studying the factors that allow *Candida* species to cause urinary tract infection (UTI), it is important to recognize that *Candida albicans* is the leading cause of fungal UTI. Accordingly, factors relating to pathogenesis of this species in the kidney and collecting system will be considered in detail. Data relating to non-*albicans Candida* are included in the discussion where available and pertinent.

The potential of *C. albicans* as a urinary tract pathogen is dependent in part on successful colonization of body sites near to or with access to the urinary tract. *C. albicans* is a normal component of the body flora and is found in 15%–60% of the population. The organism frequently colonizes the oropharynx [1], colon [2], and vagina [3] of healthy humans and can enter the urinary tract by ascending from the perineum (retrograde infection) or by hematogenously seeding the kidney and "spilling over" into the urine (antegrade infection) [4].

EXPERIMENTAL ANIMAL MODELS OF RENAL CANDIDIASIS

The fate of yeast cells entering the arterial circulation of the human kidney from elsewhere has not been directly studied, but has been inferred from animal experiments involving the intravenous (iv) inoculation of viable *Candida* blastoconidia [5, 6]. The resultant renal pathology is highly inoculum-dependent and closely resembles autopsy findings in humans with fungemia [7, 8].

Shortly after the iv inoculation of 10^3 to 5×10^6 *C. albicans* blastoconidia, the fungus is detectable in all major organs [9] especially the brains and kidneys [5, 9]. In the kidney, yeast cells penetrate through the blood vessels into both the cortex and medulla, causing an influx of neutrophils. In contrast to other organs, infection is not controlled in the kidney [5, 9, 10]. In the first 12 h, yeast forms elongate and rupture from the interstitium into the renal tubular lumen (Figure 1). Here, *Candida* species capable of producing germ tubes

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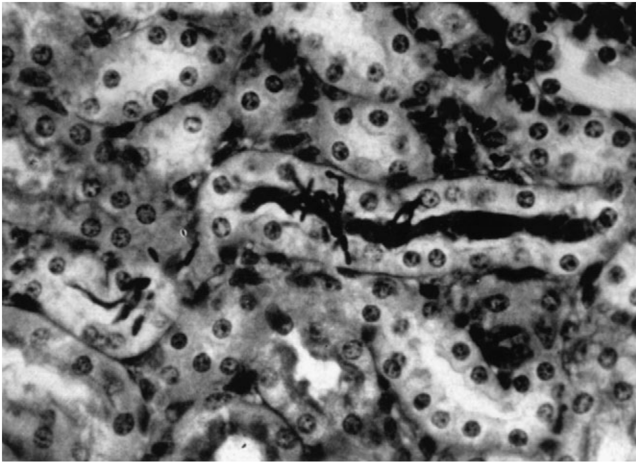

Figure 1. Photomicrograph of mouse renal tubules within the first 12 h after intravenous inoculation of *Candida albicans* blastoconidia. Elongate hyphal organisms are noted in the center tubule. (Original magnification, ×400). Kindly provided by Dr Donald Louria.

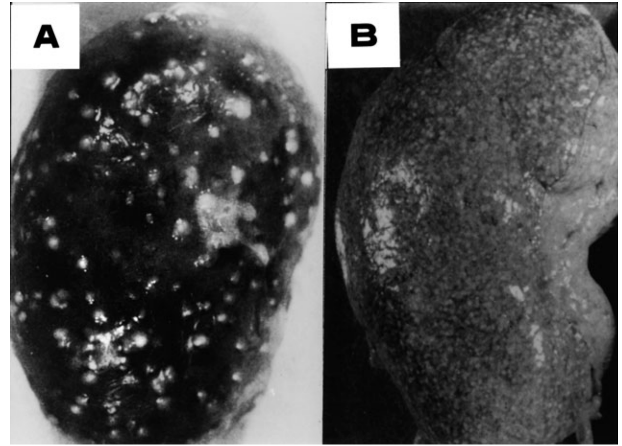

Figure 2. *A,* Gross photograph of rabbit kidney 4 days after intravenous inoculation of *Candida albicans*. Reprinted with permission From Elsevier [11] and Dr Frank C. Odds. *B,* Gross post-mortem photograph of human kidney from a patient with disseminated candidiasis. Reprinted with permission from Wolters Kluwer [12].

markedly proliferate and elongate. Mycelial casts are washed into the medulla and caught in the loops of Henle or the collecting tubules. The elongated hyphae then rupture back into the interstitium and produce a predominantly mononuclear inflammatory response. The hyphae become fragmented and gradually disappear.

Two weeks after iv challenge, only cellular cortical scars remain. High inocula cause renal failure and early death in the animals, and at autopsy, the kidneys are studded with abscesses. The latter is not an uncommon finding in patients with bloodborne candidiasis (Figure 2) [12]. In mice, progressive sepsis and not renal failure is the main cause of death [13]. A sublethal inoculum produces so-called excretory lesions confined for the most part to the renal pelvis, collecting tubules, and proximal ureters. Pyramid tips may become necrotic and, along with masses of tangled hyphae and yeasts (fungus balls or bezoars), fill the renal pelvis and may obstruct the collecting system (Figure 3). Identical lesions have been described in human cases, further suggesting that the pathogenesis is similar to that described in animal models [8] (Figure 4).

Progression of metastatic foci of *Candida* species is held in check in the liver and spleen but not in the renal parenchyma. Such uncontrolled proliferation of *Candida* species in the kidney was thought to occur because the fungi found a relatively safe haven for growth in the tubules and collecting system [5]. However, this conclusion is most likely an oversimplification as our understanding of the molecular biology of *Candida* grows. The genotypic and phenotypic complexity of *Candida* species as they interact with the renal environment is becoming increasingly apparent.

Although both the innate and adaptive immune system are vigorously activated in kidney infection by *C. albicans*, it is primarily the innate immune response to an iv challenge of the organism that determines the extent of renal pathology in the murine model [16] and perhaps in humans, as well. The cell walls of *Candida* blastoconidia, richly endowed with linear and branched β-glucans, bind Dectin-1, a C-type-lectin-like receptor expressed mainly on myeloid cells. The binding in yeast is most evident in the region between the parent cell and the mature bud. Dectin-1, in conjunction with Toll-like receptors (TLR) activate NF*K*B in macrophages. This cytosolic transcription factor, in turn, causes release of inflammatory cytokines such as tumor necrosis factor (TNF)–α and triggers production of reactive oxygen intermediates and killing of phagocytosed yeast.

Within 12 h after iv infection, keratinocyte-derived chemokine (KC), the murine analog of human CXCL8/IL-8, is produced by macrophages in the kidney interstitium. KC functions principally as a chemoattractant of neutrophils to the site of *Candida* infection working in concert with macrophage inflammatory protein-1-β. These chemokines are transcriptionally regulated by signalling through TLR2, TLR3, and TLR4, which recognize *C. albicans* polysaccharides. KC levels in the renal parenchyma continue to correlate strongly with progression of infection at 24 and 48 h [16]. Thus, in the mouse model, kidney tissue damage is related in a quantitative fashion to the innate host response.

Hyphal filaments, however, fail to bind Dectin-1 and thus do not produce these responses [17]. It is purely speculative whether the morphologic change from the yeast to the filamentous form and the location of the latter in renal tubules is a protective response of the organism to modulate the ensuing inflammatory reaction. Nevertheless, there is no "safe haven" in the renal tubules for filamentous organisms. It has been shown

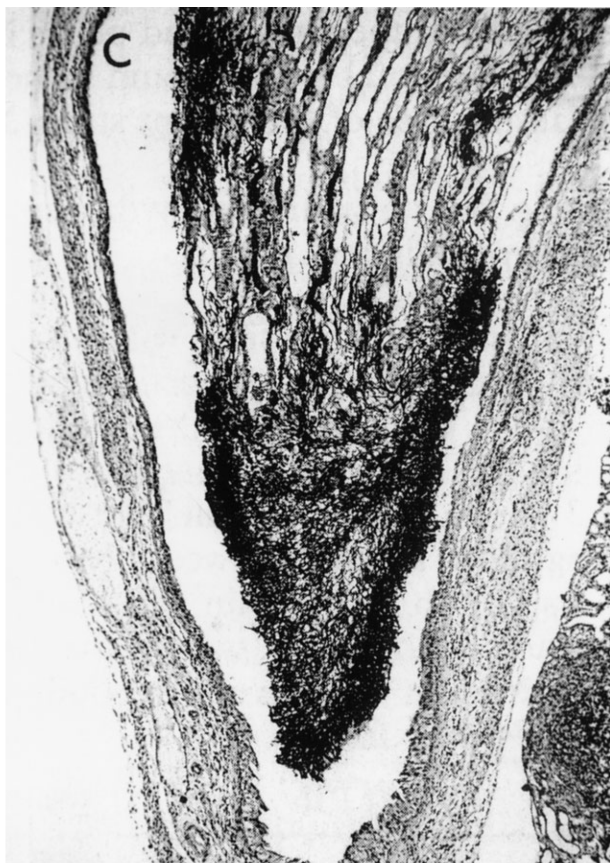

Figure 3. Photomicrograph of a section of kidney from mouse inoculated with 10_6 *Candida albicans* yeasts showing papillary necrosis with a "Cap" formed by a tangled mass of hyphae replacing the tip of the papilla (Original magnification, ×36). Reprinted with permission of Taylor & Francis [15].

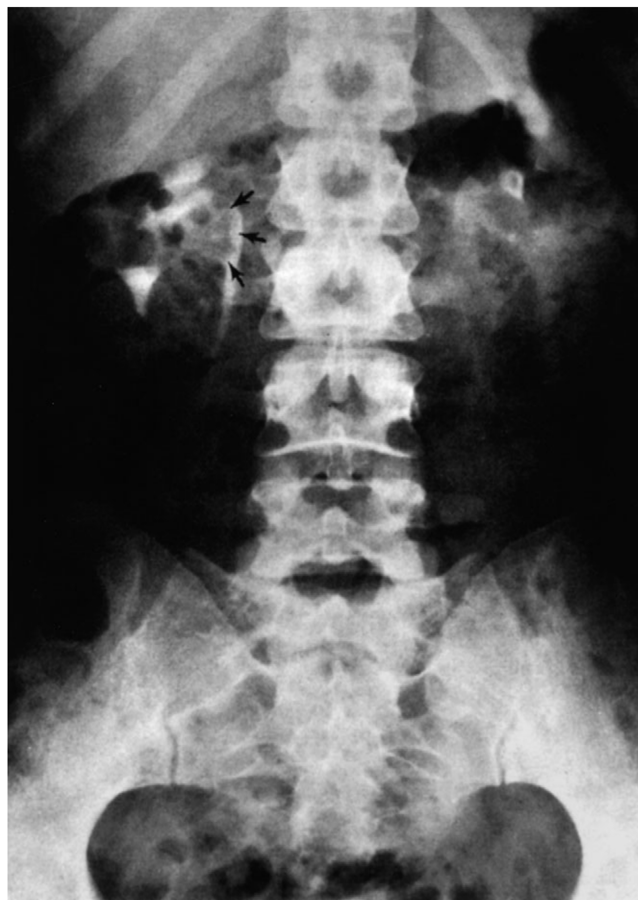

Figure 4. Excretory urogram showing radiolucent mass in right renal pelvis *(arrows)* from a diabetic patient passing particulate material in urine found to be a *Candida albicans* fungus ball. Reprinted with permission from Wolters Kluwer [14].

that the kidney responds to infection by *C. albicans* with a core response consisting of (1) an acute phase response, and (2) activation of the complement and coagulation cascades [9]. In fact, the proximal tubular epithelial cells may be an important component of the general response to the fungus for the up-regulation of cytokines and chemokines [18].

The adaptive immune system response to *C. albicans* infection in the kidney appears to be Th-2-predominant and is linked to a fatal outcome [19]. Th-2 CD4 T cells secrete cytokines interleukin (IL)–4, IL-5, and IL-10 when B cells present specific antigens to them. IL-10 is known to strongly inhibit selected immune defenses against *C. albicans* in susceptible mice in part through the down-regulation of nitric oxide production by phagocytes [10, 20]. The Th-2-mediated attenuation of the inflammatory response may well explain why renal candidiasis tends to be progressive. Interestingly, iv challenge with a mutant *C. albicans* incapable of producing hyphae induces a Th-1 response with production of interferon (IFN)–γ, TNF-α, IL-1β in the kidney with low or no mortality and control of the infection [10].

It is worth noting that *Candida glabrata*, a species that cannot produce hyphae, is responsible for up to 20% of *Candida* UTIs and may represent an increasing cause of fungal UTI in specific patient groups [21]. *C. glabrata* produces a chronic, non-fatal infection with recovery of organisms in the kidney in mice after an iv inoculation. In contrast, systemic infection with *C. albicans* results in rapid mortality with a much higher organism burden in renal parenchyma [19]. The adaptive immune response in the kidney to this "hyphae-less" yeast is strikingly similar to that found in the murine model of disseminated candidiasis for the mutant *C. albicans* incapable of producing hyphae [10].

Candida colonization of mucosal sites ordinarily poses no threat to the health of the host. Problems develop when the body's defenses are abridged as occurs with diabetes, human immunodeficiency virus infection, neutropenia, and immunosuppression accompanying organ transplantation or when patients undergo certain procedures, such as bladder catheterization or urologic surgery [22]. Breaches in defense allow increased colonization of mucosal surfaces and sometimes

candidemia, in which case the organisms can be carried to the kidneys [23, 24]. These predisposing conditions permit the survival of bloodborne or locally invasive yeast in sufficient numbers to evade the local or systemic immunity. However, a final common pathway with a particular immune defect leading to pyelonephritis or infection of the collecting system has not yet been identified. Moreover, its imminent discovery seems unlikely given the complex interaction expected among various *Candida* species, the kidney and urothelium, and the innate and adaptive immunity.

Nevertheless, on occasion valuable new insights about systemic defenses and their defects emerge. For example, the important role of IL-17A in protecting mice from an intravenous challenge of *C. albicans* was recently demonstrated. Huang et al [25] noted the induction of murine IL-17A when animals were given doses of *C. albicans* blastoconidia ranging from 2 x 10^5 to 1 x 10^6 yeast/mL. A 25-fold increase in fungal burden in the kidneys occurred in genetic knockout mice incapable of the IL-17A response. Whether a similar blunted or absent cytokine response promoting *Candida* pyelonephritis occurs in humans remains to be determined, but such discoveries open up new avenues for investigation.

VIRULENCE FACTORS OF *CANDIDA ALBICANS*

C. albicans utilizes a number of virulence factors which allow it to colonize tissue and disseminate. These operate in concert with expression of specific factors varying at different stages during a *Candida* infection.

Genetic Diversity

The recognition of the phenotypic and genotypic dissimilarity among *Candida* strains found in different anatomic locations has extended understanding of the pathogenesis of candidiasis. Soll et al [26] compared DNA patterns of isolates from the mouth, vagina, or rectal area of healthy women. One half of the women were colonized by *Candida* simultaneously in >1 of these areas, but isolates from different sites were either genetically unrelated or highly similar but not related. The data suggested that *Candida* organisms adapt to different anatomic locations and that there may be strains which preferentially colonize the vagina, oropharynx, and anorectal area. Similar results have been found for some patients with recurrent candidiasis as well. Schmid et al [27] found reduced genetic diversity among infecting candidal strains in patients with AIDS who had recurrent thrush, compared with oropharyngeal isolates from healthy individuals. Similar observations were made in a study of *Candida* vaginitis [27]. Thus, there appears to be at least some tissue tropism with respect to both colonization and disease for *Candida* species. We could find no data for the urinary tract. Studies in this area might reveal whether, like *Escherichia coli* [28, 29], there are uropathogenic strains of *Candida*.

Adherence

C. albicans is capable of adhering to a broad range of tissues and inanimate surfaces. For example, the yeast can bind to buccal and vaginal epithelial cells and corneocytes, as well as to cultured cells (HeLa and HEp-2) [30]. Adherence to the surfaces of indwelling urinary catheters and a range of plastics has also been demonstrated and may contribute to the subsequent infection of the urinary tract (Figure 5). Adherence is considered a crucial virulence attribute, because it allows the yeast to attach to body sites and commence proliferation [32]. Mechanisms allowing attachment are particularly important in sites where there is secretion of mucous (vagina), shedding of cells together with

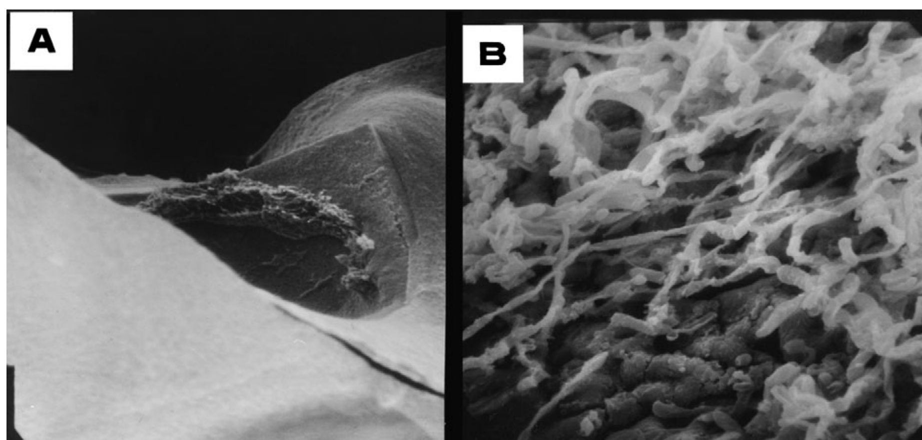

Figure 5. Scanning electron photomicrograph: cross-section of bladder catheter removed from an intensive care unit patient with persistent candiduria showing a section of latex bladder catheter with a fungal mass of *Candida albicans* hyphae adherent to lumen (*A,* original magnification, ×325) and a tangled mass of *C. albicans* hyphae in a catheter lumen (*B,* original magnification, ×1250). Copyright © 2000 by Current Science Inc. Reprinted with kind permission of Springer Science+Business Media [31].

production of saliva (oral cavity), or fluid flow (urinary tract). Infecting yeast must overcome the natural clearance mechanisms associated with these locations. There is strong evidence that *C. albicans,* with its effective adherence properties, tends to be highly pathogenic, whereas species that adhere poorly, such as *Candida krusei,* display low infectivity [33].

The adherence of a yeast to a human mucosal or endothelial cell may be viewed as the first interaction between the fungus and the host and the successful contact will affect the subsequent colonization of surrounding tissue and perhaps dissemination throughout the body. Adherence is achieved by a combination of specific and nonspecific mechanisms [32]. It is now believed that attachment and adherence of *C. albicans* depends on at least 4 recognition systems [34]; these can be classified according to the type of adhesin, host cell type (epithelial, endothelial, or platelets), and the chemical composition of the host cell ligand (protein or carbohydrate). System I adhesin is a mannoprotein that attaches to fucosyl or glucosaminylglycosides of epithelial cells. Integrin-like receptors resembling those on mammalian cells are also receptive to yeast mannoproteins and characterize System II adhesin. The System III adhesin is mannan that uses the protein component for ligand recognition. System IV adhesin, another mannoprotein, enables *C. albicans* to colonize splenic parenchyma.

Thus, adhesins for the most part involve cell-wall proteins present on the exterior portions of *Candida* cells and have been associated with the fibrillar layer on the outer region of the yeast cell wall. The cell wall is highly dynamic during the cell cycle and depends on growth conditions. Only a limited number of cell-wall proteins have been suggested to be crucial to adhesion to human tissues. In *C. albicans*, the agglutinin-like sequence (*ALS*) genes and the Als proteins Eap1 and Hwp1 are the principal putative adhesins [35, 36]. In *C. glabrata* Eap1/6 and adhesin-like wall proteins (Awp)1/2/3/4 have been tentatively identified [37]. Not only are they specific for target molecules on host cell surfaces, but also they may adhere to extracellular matrix proteins, including laminin, fibronectin, and collagen [38–40].

The contribution of non-specific adherence mechanisms to the overall colonization process is smaller than the specific mechanisms, but they operate over a larger distance [32]; these include cell surface hydrophobicity, electrostatic charge, and van der Waals forces. Like human cells, yeasts display a net negative charge and this must be overcome before specific adherence can take place. Cell surface hydrophobicity is an important element of the nonspecific adherence mechanisms and undoubtedly influences the behavior of *C. albicans* in the aqueous environment of urine and blood. Hydrophobic *Candida* cells are more adherent than hydrophilic cells to a variety of host tissues including the kidney [41, 42]. The ability of *C. albicans* to modify cell surface hydrophobicity is related to conformational changes in surface mannoprotein fibrils [43, 44] with lengthening the acid-labile but not the acid-stable β-1,2-oligomannoside chains [45, 46].

With respect to the pathogenesis of *Candida* cystitis and retrograde infection of the urinary tract, relatively little information is known. *C. albicans* has been shown to attach to exfoliated human uroepithelial cells, and this response can be blunted by preparing the cells in a solution of mannose and enhanced by mixing the cells with piliated Enterobacteriaceae [47]. In a tissue explant assay, *Candida* adherence studies were performed on bladder mucosa removed from pathogen-free, New Zealand white rabbits [48]. The authors showed that *C. albicans*, *Candida tropicalis*, and *C. glabrata* blastoconidia adhered equally well and, in an additional experiment, found that the adherence of germinated *C. albicans* was significantly better than blastoconidia. Moreover, prolonged incubation of the tissue explant with *C. albicans* resulted in denudation of the epithelium within 4 h.

Nonetheless, candidal organisms confined to existence as budding yeast remain pathogenic for the urinary tract. Indeed, *C. glabrata* accounts for 15%–20% of *Candida* UTIs [49] and obviously adapts to the urinary tract quite efficiently. In attempting to account for the pathogenicity of an organism devoid of hyphae, the answer may lie in the response of *C. glabrata* to nicotinic acid deficiency. *C. glabrata* is an NAD auxotroph relying solely on exogenous nicotinic acid for growth. In a carefully controlled murine model of ascending *C. glabrata* UTI, the privation of nicotinic acid has been shown to signal the expression of a lectin encoded by the yeast's *EPA1* gene [50] which enhances adherence to bladder mucosal cells. In addition, many patients with *C. glabrata* UTIs have an indwelling bladder catheter. Made from silicone or latex rubber, nicotinic acid levels on the surface of the device would be expected to be low. Furthermore, *C. glabrata* has recently been shown to more heavily colonize silicone in the presence of urine when compared with other non-*albicans Candida* [51]. Thus, it would not be surprising if the organism's adherence and subsequent colonization and infection of the urinary tract were facilitated not only by low levels of nicotinic acid, but even further by the presence of an indwelling catheter.

Dimorphism

C. abicans is not thermally dimorphic as are some endemic, soil-borne fungi, but it is nonetheless capable of switching from a budding yeast phase that produces blastoconidia to a pseudohyphal or hyphal form under a variety of conditions. The importance of dimorphism in the pathogenesis of invasive candidiasis has not been completely elucidated. Lacking the tools of molecular biology, the work of early investigators was necessarily descriptive in nature. Early workers repeatedly associated the hyphal form of *Candida* with pathogenicity. In 1965, Mackenzie [52] found that *Candida* blastoconidia exposed

to ultrasonically disrupted kidney cells produced far more germ tubes than did yeast exposed to sonicated liver, spleen, heart, and lung tissue, perhaps partially explaining the unique susceptibility of the kidney. The main body of opinion continued to emphasize the importance of germ tubes and hyphae for virulence.

In a provocative series of experiments, Ryley and Ryley [15] studied the pathogenicity of a strain of *C. albicans* fully capable of transformation into a filamentous form (NCPF 3153) and its "hyphae-less" mutant (CA-2). Employing inocula ranging from 10^5 to 10^7 blastoconidia in mice, striking differences in survival and histopathologic findings in the kidney were noted. The normal strain of *C. albicans* at an inoculum of 10^7cfu/mL was lethal to all animals, with a mean survival time of 1 day. Lower inocula increased survival, but death still occurred in a mean of 11.7 days in all animals given $\geqslant 10^5$ blastoconidia. In striking contrast, the hyphae-less mutant at an inoculum of 10^7 still produced death in all animals, but the mean survival of the mice in this group exceeded 13 days.

The *Candida* species without hyphae were not avirulent, but they produced vastly different histopathologic findings. Five to 24 h after infection, yeast and germ tubes could be seen in the glomerular and peritubular capillaries and the expected penetration of tubular walls was present in animals infected with the parent strain. With the mutant, germ tubes and hyphae were never seen throughout the experiment, but the yeast displayed a particular predilection for glomerular capillaries and also penetrated the tubular lumen, through some cells and between others.

By day 1, the parent strain produced small (0.1-mm) cortical abscesses. The mutant had reached the tubular lumen, but there were no abscesses. By day 2, abscesses were enlarging from the parent strain infection, and hyphae were already in the renal pelvis; but with the mutant, only small cortical abscesses had developed by this time. By day 5, both large (1-mm) abscesses and papillary necrosis had been produced by the parent strain but not the mutant. By 2 weeks, the abscesses caused by the parent strain were resolving. Fungi were no longer present in these sites but had moved downstream with hyphal masses, obstructing the renal pelvis and causing hydronephrosis exactly as had been previously described (Figure 3) [5, 6]. With the mutant, viable yeast were found throughout the kidney, but obstruction and hydronephrosis were not present.

Therefore, the hyphae-less mutant was fully capable of invasion, abscess production, tubular penetration, and persistent infection, but it was not nearly as pathogenic as the parent strain. *C. glabrata* does not produce true hyphae and cannot produce pseudohyphae except under special cultural conditions [53, 54]. It is noteworthy that this hyphae-less yeast, although capable of renal infection, only rarely produces fungal masses within the renal pelvis [55–59]. It is tempting to speculate that the pathogenicity of *C. glabrata* in bloodborne UTI might be similar to the mutant strain, CA-2.

These same authors also studied the histopathology associated with the iv inoculation of a strain of *C. albicans* capable of producing only hyphae in the mouse model. Employing the maximum inoculum (ie, 10^7 cfu/mL), which did not result in the rapid death of animals, this hyphae-only mutant produced a few cortical abscesses containing rare yeast-like forms during the first few days after inoculation. Inflammation was present for up to 2 weeks, but fungi were rarely seen beyond the first week. A single animal had gross hydronephrosis with moderate numbers of filamentous organisms in the renal pelvis. At 4 weeks and beyond, an occasional renal cortical scar was present, but pelvic lesions were absent. Apparently, mutations in *C. albicans* confining the organism to one phase or another decidedly reduce pathogenicity. Fully virulent *Candida* organisms seem to have a repertoire of morphologic responses to conditions in the kidney that appear to make the yeasts consummate renal opportunists.

The mechanisms controlling the dimorphic transition are complex and the processes involved have been implicated in the pathogenicity of *C. albicans* [60]. The traditional view had been that the budding phase of *C. albicans* represented the commensal or nonpathogenic form, whereas the hyphal form was invasive. Therefore, the switch from the budding to the hyphal form represented the move from a commensal to a pathogen. However, this is no longer considered to be the explanation, because both forms have been shown to cause disease. Moreover, molecular data do not support this assertion [60]. For example, germ tube–deficient mutants are very capable of inducing vaginitis in mice indicating that the budding yeasts are capable of causing disease. Yeast forms are also capable of invading corneocytes and cells of the gastrointestinal mucosa [30, 32]. Moreover, *C. glabrata,* a species confined to the yeast phase is second only to *C. albicans* as a cause of invasive candidiasis, including UTIs in humans [56, 57, 59].

Recent work continues to emphasize that, under certain conditions and in specific animal models, there remains a correlation between tissue invasion and germ tube formation [61]. Nevertheless, most clinical specimens contain both budding yeast and hyphal forms in *Candida* infections.

A range of environmental factors affect the transition from the blastoconidial to the hyphal mode of growth, and in the urinary tract, acid pH, proteinuria, and limited nutrients would favor the filamentous forms of *Candida*. Indeed, the rates of germination and elongation of hyphae are fastest at low pH in the presence of nitrogenous compounds—a scenario often encountered in the urine of predisposed patients [62].

Among the major contributing influences underlying the ability of an individual organism to undergo polymorphic changes according to the surrounding environment is that of quorum sensing. *C. albicans* was the first eukaryotic organism

shown to exhibit this property through a variety of secreted compounds that modify its microscopic appearance and ability to form biofilms. For example, yeast-phase *C. albicans* secrete morphogenic autoregulatory substances (MARS) [63] and tyrosol, a tyrosine derivative, which induces hyphal formation, whereas the sesquiterpenes, farsenol and farsenoic acid, also secreted by the fungus inhibit the transition [64, 65]. These substances accumulate in the local environment as the cells proliferate and are mediators of quorum sensing. Moreover, in experimental candidiasis, farnesol has been shown to blunt the expression of INF-$\gamma$and IL-2 in the kidney leading to a higher organism burden in that organ [66, 67].

Galvanotropism and Thigmotropism

Germ tubes of *C. albicans* respond to electrical fields (galvanotropism) and to changes in substrate topography (thigmotropism) by reorienting their growth axis according to local calcium concentrations [68, 69]. The reorientation of *C. albicans* hyphae in relation to electical fields is modulated by calcineurin and its action on the voltage-gated Cch1p channel, which establishes cathodal cell polarity in an electical field. Thigmotropism apparently relies on the stretch-activated, plasma membrane calcium channel Mid1. The latter may be a mechanosensor of changes in surface topography and obstacles in the path of invading hyphae. The channel is thought to permit localized calcium influx to determine a new site for hyphal elongation [70]. In addition to lengthening, hyphae are able to form sinusoidal curves and helices on semi-solid media.

These morphologic changes very likely give them the ability to adapt hyphal growth to mucosal or endothelial surface discontinuities and explore the environment in search of nutrients [71]. Possibly because of variations in actin assembly in the section of the fungus making contact with the host cell, focal germ tube growth is stimulated and the germ tube bends. Thigmotropism is important clinically because it allows *C. albicans* to grow between sheets of cells following the line of least resistance in tissue rather than attempting to penetrate directly through layers of cells [72]. Thigmotropism also facilitates growth along the intima of blood vessels. Although the kidney and collecting system undoubtedly present a variety of complex endothelial and mucosal surface discontinuities to invading *Candida*, how these organisms employ the virulence factors of galvanotropism and thigmotropism in UTI has not been established.

Phenotypic Switching

It has long been understood that no individual phenotypic trait explains the complete pathogenic potential of *C. albicans* [73]. The yeasts can switch reversibly and at a high frequency assuming several different morphotypes [74]. The changes in morphology are modulated by many environmental factors, such as temperature, pH, UV radiation, and zinc concentration [75–78]. Rather striking macroscopic evidence of the variations can be seen as changes in colonial morphology on agar. There are 2 distinctive types of *Candida* colonies, white and opaque, and the morphogenesis is closely linked with mating [79]. The high-frequency switching in *C. albicans* strain 3153 has been shown to affect several virulence traits, including susceptibility to antifungals [80], adhesion [81], proteinase activity [82] and antigenicity [80–83]. Through this property, adaptation to the micro-environment can occur more readily [76].

Phenotypic variants may differ from one another in surface components, and thereby adherence properties may be altered [84–89]. The antigenicity of *Candida* species may also change with modifications in the yeast cell surface enabling the organism to become "invisible" to bloodborne and secretory antibodies produced against the outermost layers of the original form. By the time new antibodies are produced, yet another switch event may have occurred. Isolates of *C. albicans* implicated in disease are known to switch at a higher frequency than commensal strains for reasons which are not yet understood, but prolonged culturing of invasive strains leads to a reduction in switching ability [90].

The decreased susceptibility of phenotypic variants to killing by phagocytes and oxidants has been demonstrated at least in vitro [89], raising the possibility that virulence could be enhanced in vivo [76]. High-frequency switching provides *C. albicans* with a second level of phenotypic variability over and above that of germ tube formation. Such adaptation could be basic to propagation and survival in an ever-changing environment such as the kidney. In this way, *Candida* species may be able to present a range of cell types to the host's urinary tract.

Few data specific to *Candida* UTIs are available with respect to phenotypic switching. However, Kvaal et al [82] were able to show that white phase cells of *C. albicans* strain WO-1 colonized the kidney to a greater extent than opaque cells in a murine model of disseminated candidiasis. Whether such an adaptation by *Candida* occurs in the confines of the human kidney during disseminated infection is unknown.

Data regarding *Candida* cystitis are likewise not available, but vaginal colonization by *Candida* undergoing phenotypic switching has been demonstrated [91]. Such adaptive colonization could provide the organism a portal of entry for ascending UTI. Nevertheless, compelling evidence for the role of switching is lacking for either vulvovaginal candidiasis [92] or bladder infection.

Hydrolytic Enzymes

Secreted Aspartyl Proteinases. *C. albicans* is capable of producing a range of hydrolytic enzymes that facilitate adherence to host tissue, rupture of cell membranes, invasion of mucosal surfaces and blood vessels, and evasion of the host's immune

response [24]. Secreted aspartyl proteinases (SAPs) are principal among such enzymes and degrade proteins related to structural and immunologic defenses, such as collagen, keratin, mucin, antibodies, complement, and cytokines, during tissue invasion [93–95]. Although *C. albicans* is the highest producer of SAPs, these proteinases are present in *C. tropicalis*, *Candida parapsilosis*, and *Candida dubliniensis* but not in *C. glabrata* [96–99].

At least 10 SAPs are known to exist, and each may function differently to enhance the infectious process [94]. SAP 2, expressed predominantly by yeast cells, has especially broad substrate specificity and consequently has been the subject of several investigations [100]. However, the proteinase apparently is not continually produced. In an analysis of SAP 2 in 2 mouse models of disseminated candidiasis, Staib et al [101] showed that *C. albicans* expresses the enzyme only in targeted organs such as the kidney. Organs from which the bloodborne infection originated showed no trace of SAP 2. The authors concluded that SAP 2 was required for the later stages of an infection as might occur in the kidneys but not for initial invasion. Furthermore, there is a clear association between proteolytic activity and strain virulence, because mutant strains of *C. albicans* deficient in the secretion of SAPs are less lethal in murine models and colony counts in the kidneys are reduced [102].

Additional insight into the potential role SAPs might play in urinary tract candidiasis was gained in the study by Fallon et al [103]. These investigators employed pepstatin A, a protease inhibitor that specifically inhibits aspartyl proteinases. The administration of this substance to mice infected with *C. albicans* blocked the colonization of the kidney altogether, indicating the requirement of the organism to produce SAPs for infecting this organ. It should be noted that the study neither distinguished among individual SAPs in the infectious process nor specifically examined a retrograde model of *Candida* UTI.

The production of SAPs varies among *Candida* species, with *C. albicans* being the most pathogenic and producing the highest levels. For example, *C. albicans* isolates implicated in cases of vulvovaginal candidiasis have been identified as high producers of SAPs [73, 104]. In particular, SAP 1 and 3 have been shown to be produced in patients with both active and recurrent vulvovaginal candidiasis. Low producers, such as *C. parapsilosis,* are less pathogenic [105]. Reduced SAP production may provide a partial explanation why this species is less frequently encountered in *Candida* UTIs. Reports have also demonstrated that SAPs are capable of cleaving sIgA [95], which is an important component of vaginal immunity. Loss of vaginal sIgA theoretically could promote colonization of the female urinary tract by *Candida* species and subsequent ascending infection.

Phospholipases. Phospholipases hydrolyze mainly glycerophospholipids, which are major components of mammalian cell membranes. The hydrolase activity cleaves fatty acids from phospholipids thereby destabilizing the membranes. These enzymes are divided into four classes depending upon the sites of attack [106]. *C. albicans* produces all 4 extra-cellular phospholipases (A–D), all of which have the ability either to lyse biological membranes or of altering the nature of the host cell surface, possibly facilitating adherence and colonization [107, 108]. Phospholipase B-type enzymes have multiple capabilities and have been directly linked to pathogenicity [108, 109] in contrast to the others [108, 109]. *C. albicans* contains several phospholipase B-encoding genes, and the highest expression levels of these genes are observed in the hyphal and pseudohyphal phases of the fungus [106]. Indeed, the highest phospholipase activity is concentrated where hyphae are in direct contact with the cell membrane [110]. Extracellular phospholipase activity has been recently demonstrated in non-*albicans Candida* species, but in significantly lower amounts [104].

With respect to pathogenesis in the kidney, knockout phospholipase B-deficient isolates are clearly less invasive than parental strains with intact phospholipase B activity [109]. In a murine model of disseminated candidiasis comparing the 2 for virulence, grossly visible renal abscesses could be produced only with the parental strain and all mice infected with this strain were dead in ≤9 days. In contrast, 60% of the mice challenged with the knockout strain were alive. Scanning electron microscopy indicated that the parent strain had much greater ability to penetrate both epithelial and endothelial monolayers than the knockout strain. The investigators sought to show that the enhanced lethality observed was due to phospholipase activity and resultant direct host cell injury and renal tissue penetration. With use of immunohistochemical staining, the authors were able to show that the enzyme was present in the kidney after infection with the parent strain but not with the mutant [109]. Vitullo et al [111] demonstrated that *C. albicans* cells harvested from the kidney infected with the phospholipase-producing parent strain were coated with anti-phospholipase B antibodies, indicating in vivo excretion of the enzyme. These antibodies were not present on the cells of the phospholipase-deficient knockout found in the renal parenchyma.

Evidence of phospholipase production in human *Candida* UTIs is far from robust. In patients with candiduria, early studies showed that urine isolates of *C. albicans* secreted phospholipase B but less than blood isolates [112]. More recently, it has been noted that 72% of urinary tract isolates of *C. albicans* were producers of phospholipase—a rate that was slightly greater than that produced by blood isolates. [113]. In comparisons of candiduria due to *C. albicans* with that caused by non-*albicans Candida*, two studies from Brazil provide some insight. The first from a children's hospital revealed that, among 100 isolates of *Candida* from urine, 46 (82%) of 56 *C. albicans* strains were phospholipase producers, compared with 8 (40%) of 20 *C. tropicalis* strains and 5 (45%) of 11 *C. glabrata* strains

[114]. In another report, 5 isolates of *C. tropicalis* from patients in an intensive care unit exhibited phospholipase production, which the authors postulated might suggest that more invasive organisms might occur among sicker individuals. However, there was no clinical information in these studies allowing the reader to distinguish renal candidiasis from lower UTI or infection from colonization of the collecting system. Nevertheless, organisms producing phospholipases are clearly associated with candiduria due to various species and perhaps with *Candida* UTI.

Hemolysins. Hemolysins are enzymes that induce the rupture of red blood cells. Hemolytic activity is important for in vivo microbial growth because, in the process, hemoglobin—a rich source of iron— is released [115]. Essential for growth of *Candida*, free iron sources are very limited in the body, because most iron is sequestered by host proteins, especially transferrin [116]. Thus, hemolysins secreted by *Candida* would replenish the organisms' supply of iron from hemoglobin. A variety of *Candida* species produce $\geqslant$1 α or β hemolysin, with *C. albicans* and *C. dubliniensis* being the greatest producers [117, 118], and production may increase in the presence of elevated blood glucose concentrations [117–119]. The putative gene involved in expression of *Candida* hemolysin is *HLP* [120]. The role of hemolysins in invasive disease has not been studied extensively, but a recent association with bovine mastitis has been suggested [121]. The contribution of hemolysins to survival in the kidney or in facilitating *Candida* UTIs has not been studied specifically.

Biofilm Formation

Candida biofilms are structured fungal communities attached to a surface. The individual organisms are embedded in a slimy matrix of extracellular polymers and display a phenotype which is unlike that of free-floating (planktonic) cells [122]. A mixture of morphological forms (ie, yeasts, hyphae, and pseudohyphae) is ordinarily present in 2 distinct layers: a thin, compact layer of yeast forms underlying a thicker, more open hyphal layer. *Candida parapsilosis*, *Candida pseudotropicalis*, and *C. glabrata* consistently produce less biofilm than does *C. albicans* in vitro. Biofilm is critical to candidal growth on biomedical devices, such as urinary catheters that are composed of latex coated with silicone elastomer. Both of these compounds have been shown to support more biofilm production than either polyvinylchloride or polyurethane [123].

The organisms present are notoriously resistant to azole antifungal agents [123]. Lipid formulations of amphotericin B and echinocandins demonstrate some antifungal activity against *Candida* biofilms, but their pharmacokinetics would limit their use in patients who have indwelling catheters [124]. Therefore, candiduria in patients with chronic indwelling catheters would most likely emanate from organisms previously embedded in a biofilm and not from an infection of the upper or lower urinary tract requiring treatment. Moreover, antifungal therapy would be expected to fail to clear candiduria as long as the catheter is in situ. The biofilm on bladder catheters could lead either to a refractory nidus of candidal infection [122] or to rather inconsequential candiduria serving to confound physicians trying to assess critically ill patients [122]. (Figure 5).

Evasion of the Immune Response

In addition to destruction of immunoglobulins by SAPs, cells of *C. albicans* can bind platelets via fibrinogen ligands in the bloodstream, resulting in the yeast being surrounded by a cluster of platelets which may have the effect of camouflaging them from the immune system during dissemination [125]. It is a testimony to the innate and adaptive immune system of humans that chameleon-like fungi like *Candida*, armed with such a variety of virulence attributes, do not cause more suffering than that which has been observed.

STAGES IN THE PATHOGENIC PROCESS

The ability of *Candida* to cause disease in the kidney or collecting system depends on $\geqslant$1 of the virulence factors discussed above, allowing the yeast to adhere to endothelial or urothelial cells, colonize the local area, evade the immune response, and ultimately invade tissue or disseminate to distant sites within the body. The extent of colonization and subsequent dissemination will depend upon the degree of immune malfunction in the host, the inoculum of yeast entering the bloodstream, and the antifungal agent administered [126, 127]. Given the pluripotent nature of *Candida* species, a plausible 5-phase scenario of *Candida* pathogenesis is proposed.

Phase 1

In the initial phase of infection candidal organisms must adhere to host tissue; this can be achieved by using specific or nonspecific adherence mechanisms discussed earlier. Adherence is critical to successful infection; otherwise, the yeast may be washed away in the urine flow. Adherence may be facilitated by the action of phospholipases damaging the surfaces of cells and exposing receptors to which *Candida* species may bind. During this phase, organisms capable of producing hyphae or pseudohyphae will germinate. These filamentous structures grow along the surface of the tissue and begin the process of colonization and/or biofilm formation [24].

Phase 2

In the second phase of the infectious process, the invasion of tissue commences. Hyphae may begin to burrow through layers of cells using their galvano- and thigmotropic responses. Previous work has demonstrated that *C. albicans* hyphae usually follow the path of least resistance through tissue. Inevitably,

some host cells will be invaded, leading to cell death, and the release of cellular contents will evoke an immune response. The penetration of tissue is facilitated by the action of phospholipase which can rupture cells. SAPs are capable of degrading extracellular matrix proteins and cleaving immunoglobulins, thereby thwarting a large portion of the local immune response. Although hyphae may commence the invasion process, clinical samples usually show both budding yeast cells and hyphae in infected tissue, so a degree of inter-conversion is probably operative in tissue colonization. In renal parenchymal lesions, both yeast and hyphae may be present, but only the hyphae have been shown to be capable of penetrating tissue [15].

Phase 3

In this phase, *Candida* species continue to penetrate through tissue and eventually encounter a blood vessel. Entry to the bloodstream is essential for the fungus if widespread dissemination is to be achieved. The vessel may be ruptured by physical pressure of the growing hyphae or by the action of hydrolytic enzymes. For example, SAP-2—but not SAP-1 or SAP-3—facilitates the ability of *C. albicans* to damage vascular endothelial cells and promote the entry of the organism into the bloodstream [128]. Damage to endothelial cells may also induce the phagocytosis of yeast cells where they may be carried to distant sites via the circulation in a sort of "Trojan horse" phenomenon [129].

Phase 4

Upon entry to the bloodstream, metastatic hematogenous dissemination by *Candida* organisms can commence. Single cells or hyphal filaments may be transported in the blood, but both types will be subjected to an immune response during their time in the circulation. Hemolysin activity may allow the acquisition of iron for growth from the rupture of erythrocytes while the process of phenotypic switching allows the fungus to camouflage its presence by altering the antigenicity of its cell wall. Cells of *C. albicans* are hydrophobic and will often form clumps in the blood to lessen their exposure to the aqueous environment. In addition, fungal cells will often be surrounded by platelets—a process that further minimizes their visibility to the immune system.

Phase 5

In the final phase of dissemination, the yeast may adhere to the wall of another blood vessel and begin the process of penetrating the wall and colonizing underlying tissue. Cells of *C. albicans* can induce their own phagocytosis by vascular endothelial cells which ultimately damages the endothelial cell and facilitates their egress from the bloodstream [129]. The ability to invade tissue will depend upon the overall immune status of the host and the suitability of the specific microenvironment for fungal growth.

Antegrade Infection (Hematogenous Renal Candidiasis)

The fungal burden in the host and the conditions under which cells have grown affect the ability of *Candida* organisms to colonize the kidneys in animal models [126]. To infect the kidneys, *Candida* organisms must pass directly from the renal artery via the afferent arterioles to the glomerulus and then to the renal tubules. In this scenario, the presence of fungal cells in the urine may be detected clinically, but persistent colonization of kidney tissue may be more difficult unless the fungal cells can withstand the flow of glomerular filtrate, exit the cortical or juxtamedullary nephron, and invade the renal cortex or renal medulla, respectively.

The interaction of bloodborne yeast with the glomerulus may well be much more than passive travel in circulation through renal cortical vessels. There is evidence that β-1-3 glucan, the major cell-wall component of *Candida*, can directly injure glomerular endothelial cells through the induction of free radicals [130]. Furthermore, in an animal model of *Candida* UTI, invasion of the glomerular tufts and peritubular capillaries was followed by invasion of the proximal and distal tubules, respectively. Fungal casts were detected in the urine of the animals giving further evidence of tubular invasion [131]. The biological function of the kidney (ie, filtration of blood) serves to make it a particular target for *Candida* infection, because the filtration process may act to concentrate fungal cells in renal tissue in densities not found in other organs. Clearly, the ability of *Candida* species to cause antegrade infection depends on a highly complex interaction of fungal organisms with the highly specialized renal parenchyma. The precise mechanisms involved require further elucidation.

Teleomorphs of several *Candida* species have been recently recognized as capable of producing bloodstream infection in immunocompromised patients [132, 133]. Presumably, the kidney was a target organ in these individuals, but no isolates from urine were reported. An elderly man receiving chemotherapy for non-Hodgkin lymphoma developed a urinary tract infection due to *Pichia ohmeri* (teleomorph of *Candida guilliermondii*). The patient may well have had an antegrade infection, because he also had fever and flank pain, but results of blood cultures were not given. It is not clear from these reports or from experimental infections whether there are differences in virulence between anamorphs and teleomorphs in the urinary tract [134].

Retrograde Infection (Ascending Urinary Tract Candidiasis)

The pathogenesis of retrograde infection of the urinary tract by *C. albicans* in most instances begins in a predisposed patient such as a diabetic, a hospitalized individual, or a woman with vulvovaginal *Candida* infection [135, 136]. As common as these predisposing factors are, one would expect a greater frequency of candidal cystitis than occurs. *C. albicans* can colonize urothelial cells, although 50% less well than buccal epithelium, and this

adherence, too, can be blocked by mannose [47]. Nevertheless, candiduria remains rare in structurally and functionally normal urinary tracts even among predisposed patients. The defenses operative near the portals of entry in males and females include normal flora, which may suppress *Candida* infection, as well as secretions from the prostate and female periurethral glands, which are reportedly fungistatic [137].

Successful bladder colonization and infection with *Candida* species most likely requires a significant breach of these microbiologic and physiologic barriers, as occurs with urinary stasis or the presence of a foreign body. An indwelling latex catheter becomes a conduit for the entry of organisms, including *Candida* organisms. A colonized bladder catheter may also act as a reservoir for the spread of *Candida* organisms along the urethra and into the bladder. Yeast colonizing the bladder can lead to cystitis.

Few studies of the pathogenesis of retrograde urinary tract candidiasis are available. A particularly enlightening study of some of the mechanisms of ascending *C. albicans* UTI was performed in the rat [138]. In this experimental model, 2 of the most common predisposing conditions to candidal infection were produced—namely, diabetes and pseudoestrus. Animals were challenged iv, intravaginally, or by bladder inoculation with either blastoconidia or germinated *C. albicans*. All animals given 10^5 of blastoconidia by the iv route developed renal infection. Diabetic rats had grossly visible cortical abscesses similar to those described earlier. Injection of 10^6 cfu of *Candida* organisms into the right kidneys of 4 animals produced bilateral renal infection even when the left ureter had been transected and ligated. Infection in the opposite kidney could only have been the result of candidemia. Candidemia and candiduria were demonstrated in all animals.

Of critical importance, after inoculation of 10^6 blastoconidia into the vagina of either normal, diabetic, or rats with pseudoestrus, spread to the urinary tract failed to occur. Irrespective of whether germinated or ungerminated forms of 2 different strains of *C. albicans* were used, when 10^2 cfu were injected into the bladder lumen, sustained candiduria developed only in diabetic rats. In striking contrast to these findings, the authors observed that in animals with established *E. coli* UTI, bladder inoculation of even low numbers of yeast resulted in candidal pyelonephritis. Control animals or those with established enterococcal UTI did not develop renal infection, and yeast adhered poorly to the bladder.

These unique studies warrant at least 2 conclusions. First, host factors, such as diabetes or vaginal candidiasis, by themselves failed to promote an ascending *Candida* UTI in the rat. Second, the presence of an ascending infection by a fimbriated strain of *E. coli* dramatically increased the susceptibility of the entire urinary tract and bloodstream to *C. albicans* infection in this experimental model. These findings are concordant with the in vitro observations of Centeno et al [47] that certain strains of *E. coli* and heavily piliated *Klebsiella pneumoniae* may act as a bridge between *Candida* and epithelial surfaces, promoting first a foothold and ultimately invasion (Figure 6). The significance of these studies awaits further clarification.

C. albicans adheres poorly to bladder mucosa, but under conditions of urinary tract obstruction, concomitant bacteriuria, or profound immunosuppression, penetration of the bladder wall may occur and migration into the ureter and possibly the kidney may follow [11, 21, 138, 139]. In a rat model of urinary tract infection, it has been demonstrated that concomitant infection of the bladder with a mannose-binding strain of *E. coli*–enhanced *C. albicans* agglutination and adherence to the bladder mucosa and promoted ascending UTI [139]. Enteric bacteria, such as *E. coli* and *K. pneumoniae,* enhance the adherence of *C. albicans* to mucosal surfaces whereas streptococci hinder the process [140]. These findings are significant, because they identify the potential for ascending fungal infections where there is coinfection of the bladder with a bacterium—a situation that may pertain to certain clinical settings, such as the presence of an indwelling bladder catheter.

The environmental pH has been shown to influence the rate of germination and elongation of germ tubes. In an acidic medium and in the presence of nitrogenous compounds, it has been observed that *C. albicans* germination is enhanced [62]—a response that may be the result of pH-regulated expression of genes essential to the organism's survival [62, 141]. Such observations would provide a partial explanation for the greater incidence of *Candida* UTI in such disease states as diabetic ketoacidosis or poorly controlled diabetes—conditions that lead to the production of an acidic urine. The enhanced germination

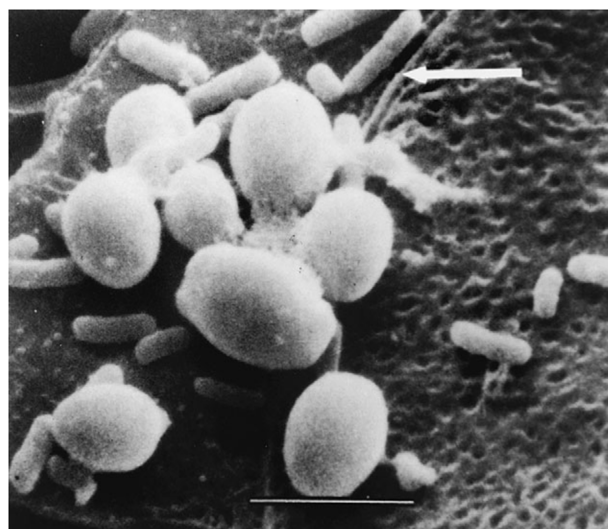

Figure 6. Scanning electron photomicrograph: buccal epithelial cells with piliated *Klebsiella pneumoniae* and yeasts. Note the juxtaposition of yeasts and bacteria. *Arrow,* cell border. *Bar,* 2.5 um. Reprinted with permission. © 1983, American Society for Microbiology [47].

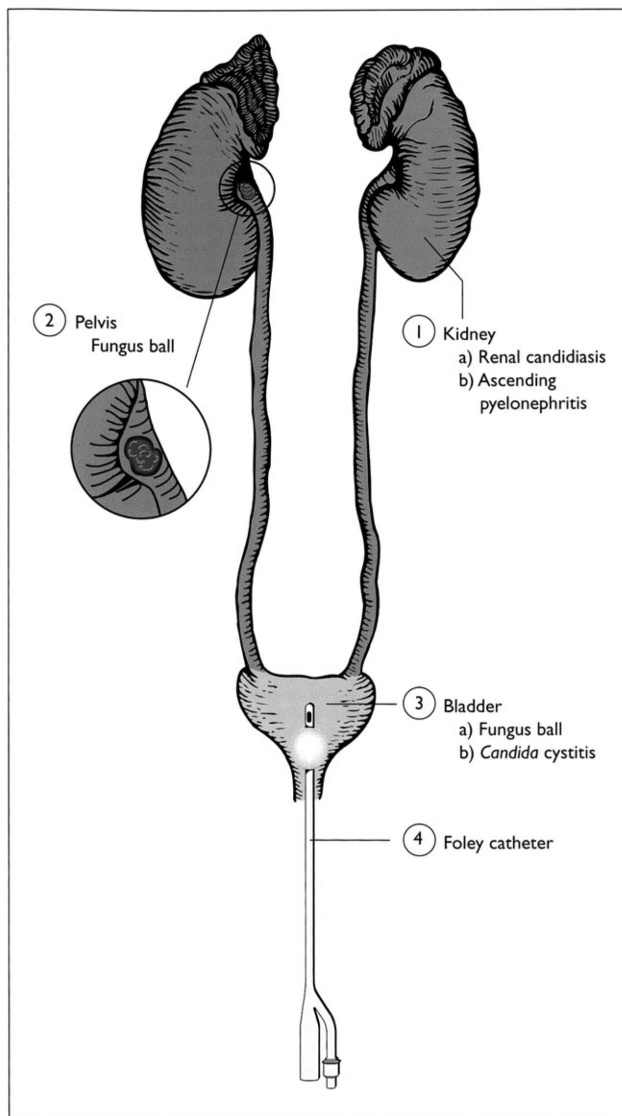

Figure 7. Anatomic sources of candiduria. Reprinted with kind permission of Springer Science+Business Media [142].

may facilitate colonization of the bladder or the urethra and possibly also contribute to an ascending infection.

The environment that the yeast encounters in the urinary tract will also influence its ability to colonize. *C. albicans* can employ a number of strategies to enable it to survive and evade an immune response. Phenotypic switching can be viewed as a potential powerful virulence factor, because it not only alters the antigenicity of the fungus, but it also affects other factors such as adherence, hydrolytic enzyme production, and germination. Different virulence factors may be used preferentially at different stages of the infectious process. For example, specific SAPs are required for each stage of infection [101], and the ability of *C. albicans* to alter its repertoire of virulence factors to disseminate and colonize is the key to its success as a pathogen. Far from being a passive opportunist, *C. albicans* can exploit favorable conditions presented by dysfunctional systemic or local defenses to survive or even thrive in the kidney or collecting system.

From the foregoing, it can be seen that candidal organisms, especially *C. albicans*, are very well equipped for colonization and invasion of the urinary tract. Nevertheless, relatively little is actually known about the regulation of expression of *Candida*'s many potential virulence factors. Signals and triggering mechanisms for genes that control phenotypic switching and the production of extracellular enzymes, such as phospholipases and SAPs, are ill-defined at present. Solid evidence is available to provide only a partial explanation of the signal pathways that regulate morphogenesis, and these have been described primarily in in vitro systems. Moreover, for the most part various signals have been studied individually. It is quite likely that infection in humans involves complex modulations of simultaneously expressed or repressed virulence factors (Figure 7).

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