Clinical and Experimental Dermatology (1982) 7, 345–354.

St John's Hospital Dermatological Society: Symposium on Genital Infections 1981

Genital candidosis*

F.C.ODDS

Department of Microbiology, University of Leicester, Leicester LE1 7RH

Accepted for publication 7 May 1981

Vaginal thrush is a condition that has been known to medicine for well over a century. Over the years it has received considerable clinical and laboratory attention. *Candida albicans*, by far the predominant cause of thrush, has been scrutinized in fine detail by biochemists, microbiologists and immunologists. A plethora of antifungals formulated for intravaginal use has been made available to combat the infection.

Yet vaginal candidosis remains one of the most common gynaecological complaints in Europe and North America. Its diagnosis is usually simple, but its treatment can be extremely difficult. There is still doubt as to the major epidemiological and pathological factors involved in the aetiology of the infection, so the reasons for failure by some patients to respond to treatment are uncertain.

Meanwhile, candidosis of the penis, which appears to have about one-tenth the prevalence of vaginal candidosis, has attracted very little research interest at all.

This article will describe aspects of genital candidosis that have been the subject of research in recent years.

Mycological investigations in the diagnosis of candidosis

The majority of cases of vaginal candidosis are diagnosed in general medical practice on clinical grounds alone, on the basis of a patient's complaint of pruritis with or without discharge. Patients who are referred for specialist gynaecological or mycological assessment are usually those who have failed to respond to antifungal treatment or who present with non-specific symptoms. For all such patients (and for patients in clinical research trials for vaginal

* Paper presented at the Edward Lewis Lecture Theatre, Middlesex Hospital Medical School, London, 2 April 1981.

0307-6938/82/0700-0345$02.00 © 1982 Blackwell Scientific Publications

candidosis) the diagnosis of thrush is regarded as valid only if a yeast, especially *C. albicans*, can be shown to be present in the vagina.

Some investigators rely exclusively on direct microscopic examination of vaginal smears for *Candida*, despite overwhelming evidence that culture of *Candida* from swabs is a much more sensitive and reliable method for detection of yeasts in the vagina (McLennan, Smith & McLennan, 1972; O'Brien, 1964; Thin *et al.*, 1975).

In my laboratory the sensitivity of swabs for the isolation of *C. albicans* has been tested *in vitro* in experiments with aqueous suspensions of *C. albicans*. A recent isolate of the fungus was grown on Sabouraud's dextrose agar (SDA) at 37°C for 18 h. The yeasts were suspended in sterile water, their concentration was measured with a haemocytometer and adjusted to 10^6 cells per ml. A series of dilutions was prepared from this stock yeast suspension.

To measure the recovery of *C. albicans* from each dilution, ten replicate sterile cotton-tipped swabs were dipped in the suspension and drained against the neck of the container. The swabs were smeared thoroughly over the surface of plates of SDA. Preliminary gravimetric determinations showed that the swabs absorbed, on average, 130 μg fluid in this procedure. To control the experiment, triplicate 130 μl lots of each suspension were therefore added to SDA with a sterile pipette and spread over the agar surface. The plates were incubated at 37°C for 48 h, and the numbers of yeast colonies that appeared were counted.

The recoveries of *C. albicans* from the swabs are shown in Fig. 1. A minimum yeast concentration of 10^3 per ml was necessary to ensure a high probability of recovery of at least one yeast colony, and yeast concentrations of 10^5 per ml or greater gave confluent growth on all plates. Recoveries when 130 μl of yeast suspensions were directly plated on SDA were almost ten times higher. This experiment confirms that swabs are a reasonably sensitive method for

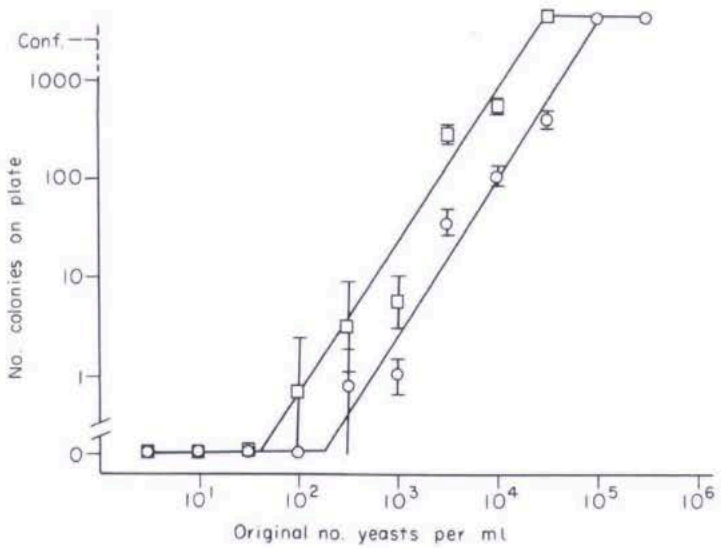

Figure 1. Recovery of colonies of *C. albicans* from swabs dipped in different concentrations of yeasts suspended in water. Graph shows means and standard deviations for ten replicate experiments with swabs and means and standard deviations for triplicate controls in which suspensions were applied to agar by pipette. Conf. means confluent growth. □ = Yeasts pipetted on agar; ○ = yeasts plated from swabs.

detection of *C. albicans*, since 10^3 yeasts per ml is a low concentration. It also suggests that a direct wash sampling method for the vagina would be an even more sensitive method for detection of *Candida*.

To measure the ability of *C. albicans* to survive on swabs, thirty-six swabs per yeast dilution were dipped and drained in *C. albicans* suspensions containing 10^3, 10^4 and 10^5 yeasts per ml. Six swabs from each dilution were immediately plated on SDA. The remaining swabs were stored at room temperature in individual sterile test tubes with non-occlusive metal caps. Six of the swabs were then plated on SDA at 2, 4, 6, 12 and 24-h intervals after immersion in the *C. albicans* suspensions. The plates were incubated and colonies counted as before.

At all three yeast concentrations tested, numbers of yeasts recovered from swabs remained essentially the same for swabs stored up to 24 h in test tubes (Fig. 2). Many physicians without direct access to laboratory facilities seem to fear that yeast viability would fall during the time required for transport of swabs from the patient to the laboratory. The data in Fig. 2 suggest that such a fear is unfounded, at least for periods up to 24 h.

Given that culture of swabs is a fair and sensitive method for the demonstration of *C. albicans* in the vagina, it remains difficult to assess the clinical significance of the fungus in the vagina in the absence of symptoms. Carroll, Hurley & Stanley (1973) provided convincing evidence that *C. albicans* is virtually never isolated from the vagina in the absence of at least mild pathological signs, which suggests that the traditional view of *C. albicans* as a common commensal in the vagina might be erroneous. However, it is clear that many females who harbour *C. albicans* in the vagina do not complain subjectively of vaginal symptoms.

Epidemiological studies of genital candidosis

Many surveys have shown that *C. albicans* may be recovered from the vagina in females without

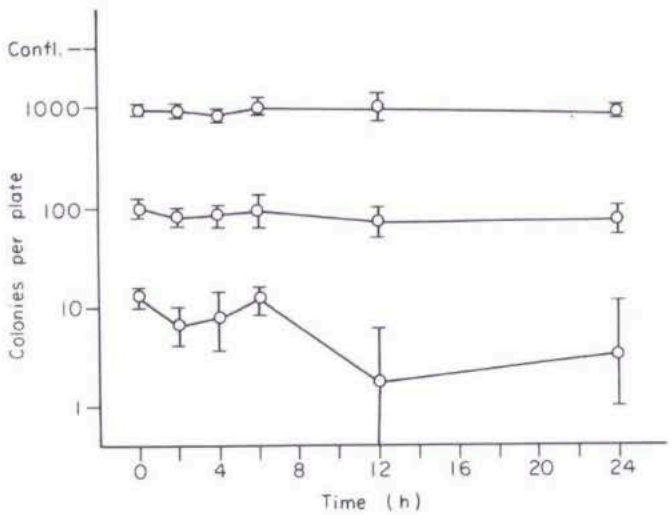

Figure 2. Recovery of colonies of *C. albicans* from swabs dipped in yeast suspensions and stored for different periods of time at room temperature. Top curve—swabs dipped in 10^5 yeast per ml; middle curve—swabs dipped in 10^4 yeasts per ml; bottom curve—swabs dipped in 10^3 yeasts per ml.

any history of pruritis or discharge: isolation rates range from about 5–10% in normal, healthy females to around 40% in pregnant females (Odds, 1979). Yeasts may also be recovered frequently from the coronal sulcus of the penis (Rodin & Kolator, 1976). The presence of *C. albicans* in the vagina is associated with a decrease in prevalence of Gram negative bacteria (Auger & Joly, 1980) and often with a pH towards the low end of the normal 4–6 range (Sautter & Brown, 1980).

The prevalence of *C. albicans* in genital sites in the absence of symptoms is generally somewhat lower than its prevalence as a commensal in the mouth or faeces (Odds, 1979) and it is therefore possible that the gut is the normal commensal reservoir for the fungus, which is spread secondarily to the genitalia. An alternative mode of spread for genital *C. albicans* is by sexual intercourse: Thin, Leighton & Dixon (1977) showed statistically that yeasts were probably spread by sexual transmission in 30–40% of cases of genital candidosis.

Until very recently it was impossible to ascertain in any particular case of genital candidosis whether the source of *C. albicans* was an endogenous site or the patient's sexual partner. The introduction of methods for differentiation of individual *C. albicans* strains (Odds & Abbott, 1980; Warnock *et al.*, 1979a) has changed this position. Warnock *et al.* (1979b) studied the *C. albicans* strain types in thirty females with recurrent vaginal candidosis. Sixteen of the patients harboured a single strain type, which was usually isolated from the mouth, anus, faeces and vagina, while the rest harboured two strain types. In all seven instances where *C. albicans* was recovered from the female's consort, the strain from the penis was the same type as the vaginal strain. It is unclear why in some cases different strain types were sometimes recovered from the faeces and from anal swabs in the same patient.

In my laboratory we have just completed a survey of *C. albicans* strain types isolated from the genitalia of more than 200 patients attending the local genito-urinary clinic. We found no significant tendency towards different strain types in males and females or in patients with and without a clinical diagnosis of candidosis (data in preparation for publication). From some of the patients, samples were also available from extragenital sites. For twelve female patients it was possible to compare *C. albicans* strain types (determined by the method of Odds & Abbott, 1980) in the mouth and vagina (Table 1). In only one instance (patient 12) was the strain from the patient's mouth different from the vaginal strain. This suggests a common source for yeasts in the vagina and the gut for most, but not all patients. Separate isolates were available from the urethra and the vagina for thirteen females (Table 1). Again, the strain types in the urethra and vagina were usually identical, but in two instances (patients 15 and 20) the urethral strains and vaginal strains differed. Considered overall, the data in Table 1 suggests a homogeneity of strain types of *C. albicans* in different sites for most patients, but there is clearly a possibility of variation in about one patient in eight.

Isolates of *C. albicans* were obtained from the genitalia of twelve males with *Candida* balanitis and their female consorts. The genital strain types were identical for eight couples, different in four (detailed data in preparation for publication). The extent of promiscuity among these couples is uncertain, but it is likely that strain differences between *C. albicans* isolates from the genitalia of the four couples mentioned was attributable to multiple sexual contacts for one or both of the partners.

Our observations on strains of *C. albicans* from different sites and consorts suggest that

Table 1. *C. albicans* strain types isolated from more than one site in twenty-five patients with vaginal candidosis. The three-digit numbers are octal codes based on the results of nine biochemical tests for each strain. Test results are usually reproducible to within one test difference (Odds & Abbott, 1980): a difference of 1, 2 or 4 between two strains for a given digit represents one test difference

Patient no.	Urethral strain	Vaginal strain	Oral strain	Rectal strain
1	377	377	277	
2	077	077	077	
3		253	353	353
4		257	257	257
5		246	246	
6		357	257	
7		157	153	
8		557	557	
9		153	153	
10		357	357	
11		157	157	
12		057	003	
13	100	100		
14	113	113		
15	057	273 + 003		
16	053	053		
17	357	357		
18	357	357		
19	057	057		
20	357	252		
21	253	253		
22	057	057		
23	657		757	
24	457			477
25	017	017		017

sources of the fungus and modes of spread vary from individual to individual, but that, in females, the most common source of *C. albicans* is endogenous.

Whatever the source of *C. albicans* in the vagina, it is evident that the fungus may persist at this site for considerable periods of time, with or without associated symptomatology. Sautter & Brown (1980) examined vaginal samples taken at frequent intervals from seven volunteers during a 4-week period. In those subjects who harboured *C. albicans*, the fungus was recovered repeatedly throughout the sample period.

We have recently investigated diurnal variations in vaginal carriage of *C. albicans*. Three

healthy, sexually active female volunteers, free of subjective vaginal symptoms, collected high vaginal swabs from themselves three times per day (on arising, at noon and at 17:00–19:00) for 5–7 days. The numbers of colonies isolated from these swabs (Fig. 3) varied over approximately a ten-fold range, and there was often a tendency towards highest colony counts in the early morning sample. Very similar diurnal variations in numbers of yeasts harboured in the oropharynx have been noted by other investigators (Gergely & Uri, 1966; Williamson, 1972a, b).

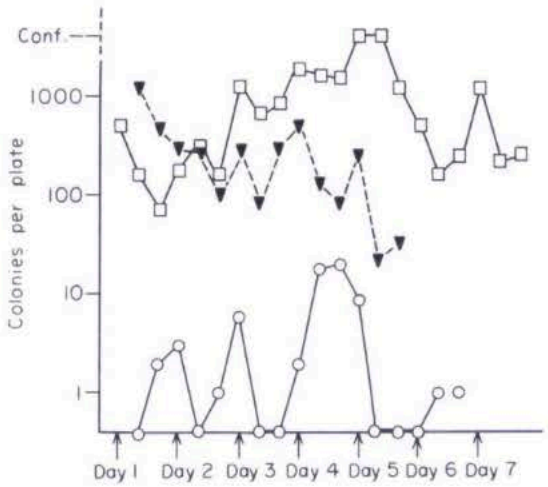

Figure 3. Diurnal variation in counts of *C. albicans* obtained from vaginal swabs in three healthy carriers of the fungus. The three curves represent the colony counts for each of the three subjects; the arrows indicate the first sample taken on each of the experimental days.

Pathogenesis of genital candidosis

Since the strains of *C. albicans* isolated from the genitalia of subjects with and without clinical candidosis appear to be the same, and since *C. albicans* can be harboured intravaginally for at least 4 weeks without subjective complaint of vaginitis, it follows that the differences between *C. albicans* as commensal and as pathogen must be determined by changes in the host, not the fungus.

Many conditions appear to predispose individuals to superficial forms of candidosis, and those that are best known and proven in the context of vaginal candidosis are pregnancy, diabetes and uncommon hormonal disorders. Although many authorities consider that antibiotic treatment for bacterial infections predisposes to genital candidosis, it is difficult statistically to separate the effects of the antibiotics *per se* from the effects of the illness that led to their use.

It has so far proved impossible to discover what changes in local or systemic factors act as a trigger to allow 'commensal' *C. albicans* to cause clinical lesions. Factors that have been proposed as local stimuli for candidosis include high vaginal glycogen levels and low vaginal pH (Cruickshank, 1934), and local occlusion of the genitalia with nylon underwear (Bull, 1969; Hurley, 1975).

Many studies have focussed attention on oral contraceptives and iron deficiencies as systemic factors that can predispose to thrush: the limitations of these studies have been reviewed by Odds (1979). There is no convincing evidence to justify the view that oral contraceptives, especially the low-oestrogen types in most common current use, have affected the population incidence of vaginal candidosis, and the elegant work of Davidson, Hayes & Hussein (1977) has effectively eliminated factors such as low serum iron and haemoglobin, or high serum ferritin as contributory factors in vaginal thrush.

The truth appears to be that candidosis of male and female genitalia occurs commonly in individuals with no underlying deficiency of the types so far considered, so that most recent experimental attention has been given to local and systemic immune factors. Secretory antibodies to *C. albicans* have been demonstrated in the vagina by several investigators (Chipperfield & Evans, 1972; Waldman, Cruz & Rowe, 1972; Warnock & Hilton, 1976), but such antibodies have been found in patients without vaginal candidosis, as well as those with symptomatic infection (Milne & Warnock, 1977). Mathur *et al.* (1977) suggested that in many instances antibodies to *C. albicans* detected in the serum of patients with thrush may be locally produced secretory IgA that has passed from the vagina into the bloodstream.

One factor likely to assist yeasts in establishing vaginal infection is the ability of the fungal cells to attach themselves to vaginal epithelia. King, Lee & Morris (1980) have shown that *C. albicans* adheres strongly to vaginal epithelia *in vitro*, and that it adheres better than other *Candida* species. This may help to explain why species other than *C. albicans* are only very rare causes of genital infection.

Treatment of genital candidosis

By far the greatest problem in the management of genital candidosis lies in its treatment. In patients for whom no amount of topical antifungals appears to make any difference to their symptoms, the misery and stress of persistent thrush can be extreme (Hurley, 1975).

There are at least seven specific topical antifungal drugs available at present in formulations that include vaginal creams, pessaries and coated tampons. All these drugs belong chemically to the polyene or imidazole derivative groups. They are all inhibitory to *C. albicans in vitro* and clinical trials suggest they are usually effective *in vivo* (Odds, 1977). However, mycological cure rates even for the best of the vaginal anticandidals are generally only in the range 80–90%, which is rather surprisingly low for local treatment of a condition that involves a single pathogen at a superficial site. The newly-marketed antifungal, ketoconazole, which has the aesthetic advantage of oral administration, also gives cure rates around 90% in thrush (Bisschop *et al.*, 1979) so it offers no real improvement in efficacy.

Several factors have been considered as explanations for chronic treatment failure in vaginal candidosis. Resistance of the infecting *C. albicans* strains to the antifungals is the least likely explanation: resistance of yeasts to polyenes and imidazole derivatives in clinical practice is so exceptional as to be negligible.

C. albicans in the vagina is commonly associated with *C. albicans* in the gut (Hilton & Warnock, 1975; Pumpianski & Ganor, 1968; Rohatiner, 1966), so eradication of yeasts from the gut by means of an oral antifungal should eliminate this potential source of reinfection in chronic

cases (Hurley, 1975). However, Milne & Warnock (1979) were unable to show any beneficial therapeutic effect when this approach to treatment was tested carefully in a double-blind trial.

The finding of *C. albicans* strains in the urethra that may be the same or different from those in the vagina suggests that the urethra may be a reservoir for reinfection after treatment in some cases, and the steadily accumulating evidence for sexual transmission of *C. albicans* and mutual symptomatic infection among sex partners emphasizes the likelihood of reinfection by intercourse. Perhaps these sources of reinfection are more important than the patient's own digestive tract. Only prospective investigation will confirm this supposition.

The effects of dosage and duration of treatment with topical antifungals in vaginal candidosis has been assessed statistically (Gough, 1979; Odds, 1977). The results suggested that the total dosage of antifungal applied is more important than any other factor in preventing recurrence of infection, and this conclusion has been confirmed in practice by the growing tendency of antifungal manufacturers to recommend short treatment regimes with high doses of antifungal for routine therapy.

It has now been shown that, at least for miconazole, a single vaginal pessary gives rise to inhibitory levels of antifungal in the vagina that persist for at least 48 h (Odds & Macdonald, 1982). If this finding applies also to other vaginal antifungals, even a single application of a sufficiently high dose would amount to a 3–4-day course of treatment (barring menstruation or douching).

Taken as a whole, these considerations amount to a recommendation for aggressive antifungal treatment of chronic vaginal thrush, which should include treatment of the male partner and the urethra to avoid possible reinfection. The treatment schedule recommended by Hurley (1975) should be eminently effective for the purpose.

Mixed infection in vaginal candidosis

One cause of chronicity of genital candidosis that has received no great attention so far is the possibility of mixed bacterial and yeast infection. Auger & Joly (1980) have shown that the presence of *C. albicans* in the vagina in patients with vaginal discharge is associated with substantial changes in the type and quantity of the bacterial microflora, and they suggest there may be a high incidence of polymicrobial vaginitis.

If this contention is true, treatment with a specific antifungal would eliminate only part of the cause of the symptoms. Perhaps more frequent use of non-specific vaginal antiseptics or mixed antifungal/antibacterial preparations would reduce the distress of what is regarded as chronic infection by *Candida* alone. There are few recent accounts of trials with such preparations. Only prospective research will reveal their true value and the extent to which vaginitis is caused by more than a single microorganism.

Acknowledgments

I would like to thank Anne B. Abbott and Karen Grunwald for their technical assistance, and Dr F.E.Willmott for providing specimens from his patients.

References

AUGER, P. & JOLY, J. (1980) Microbial flora associated with *Candida albicans* vulvovaginitis. *Obstetrics and Gynecology*, **55**, 397–401.

BISSCHOP, M.P.J.M., MERKUS, J.M.W.M., SCHEYGROND, H., VAN CUTSEM, J. & VAN DE KUY, A. (1979) Treatment of vaginal candidiasis with ketoconazole, a new, orally active, antimycotic. *European Journal of Obstetrics, Gynecology and Reproductive Biology*, **9**, 253–259.

BULL, M.J.V. (1969) Wearing tights. *British Medical Journal*, **i**, 120.

CARROLL, C.J., HURLEY, R. & STANLEY, V.C. (1973) Criteria for diagnosis of *Candida* vulvovaginitis in pregnant women. *Journal of Obstetrics and Gynaecology of the British Commonwealth*, **80**, 258–263.

CHIPPERFIELD, E.J. & EVANS, B.A. (1972) The influence of local infection on immunoglobulin formation in the human endocervix. *Clinical and Experimental Immunology*, **11**, 219–233.

CRUICKSHANK, R. (1934) Conversion of glycogen of vagina into lactic acid. *Journal of Pathology and Bacteriology*, **39**, 213–219.

DAVIDSON, F., HAYES, J.P. & HUSSEIN, S. (1977) Recurrent genital candidosis and iron metabolism. *British Journal of Venereal Diseases*, **53**, 123–125.

GERGELY, L. & URI, J. (1966) Day-by-day variation in the mycotic flora of the mouth. *Archives of Oral Biology*, **11**, 15–19.

GOUGH, D. (1979) The influence of dosage and duration of administration of miconazole on the cure and relapse of candidal vaginitis. *Royal Society of Medicine International Congress and Symposium Series*, **7**, 15–20.

HILTON, A.L. & WARNOCK, D.W. (1975) Vaginal candidiasis and the role of the digestive tract as a source of infection. *British Journal of Obstetrics and Gynaecology*, **82**, 922–926.

HURLEY, R. (1975) Inveterate vaginal thrush. *Practitioner*, **215**, 753–756.

KING, R.D., LEE, J.C. & MORRIS, A.L. (1980) Adherence of *Candida albicans* and other *Candida* species to mucosal epithelial cells. *Infection and Immunity*, **27**, 667–674.

MATHUR, S., VIRELLA, G., KOISTINEN, J., HORGER, E.O., MAHVI, T.A. & FUDENBERG, H.H. (1977) Humoral immunity in vaginal candidiasis. *Infection and Immunity*, **15**, 287–294.

MCLENNAN, M.T., SMITH, J.M. & MCLENNAN, C.E. (1972) Diagnosis of vaginal mycosis and trichomoniasis. Reliability of cytologic smear, wet smear and culture. *Obstetrics and Gynecology*, **40**, 231–234.

MILNE, J.D. & WARNOCK, D.W. (1977) Antibodies to *Candida albicans* in human cervicovaginal secretions. *British Journal of Venereal Diseases*, **53**, 375–378.

MILNE, J.D. & WARNOCK, D.W. (1979) Effect of simultaneous oral and vaginal treatment on the rate of cure and relapse in vaginal candidosis. *British Journal of Venereal Diseases*, **55**, 362–365.

O'BRIEN, J.R. (1964) Nickerson's medium in the diagnosis of vaginal moniliasis. *Canadian Medical Association Journal*, **90**, 1073–1074.

ODDS, F.C. (1977) Cure and relapse with antifungal therapy. *Proceedings of the Royal Society of Medicine*, **70**, Suppl. **4**, 24–28.

ODDS, F.C. (1979) *Candida and Candidosis*, pp. 53–62, 79–80, 87–88, 200–203. Leicester University Press, Leicester.

ODDS, F.C. & ABBOTT, A.B. (1980) A simple system for the presumptive identification of *Candida albicans* and differentiation of strains within the species. *Sabouraudia*, **18**, 301–317.

ODDS, F.C. & MACDONALD, F. (1982) Persistence of miconazole in vaginal secretions—implications for the treatment of vaginal candidosis. *British Journal of Venereal Diseases*, **57**, 400–401.

PUMPIANSKI, R. & GANOR, S. (1968) Epidemiological significance of oral *Candida* in recurrent candidal vaginitis. *Israel Journal of Medical Science*, **4**, 1268–1269.

RODIN, B. & KOLATOR, P. (1976) Carriage of yeasts on the penis. *British Medical Journal*, **i**, 1123–1124.

ROHATINER, J.J. (1966) Relationship of *Candida albicans* in the genital and anorectal tracts. *British Journal of Venereal Diseases*, **42**, 197–200.

SAUTTER, R.L. & BROWN, W.J. (1980) Sequential vaginal cultures from normal young women. *Journal of Clinical Microbiology*, **11**, 479–484.

THIN, R.N., ATIA, W.L., PARKER, J.D., NICHOL, C.S. & CANTI, G. (1975) Value of Papanicolou-stained smears in the diagnosis of trichomoniasis, candidiasis and cervical herpes simplex virus infections in women. *British Journal of Venereal Diseases*, **51**, 116–118.

THIN, R.N., LEIGHTON, M. & DIXON, M.J. (1977) How often is genital yeast infection sexually transmitted? *British Medical Journal*, **ii**, 93–94.

WALDMAN, R.H., CRUZ, J.M. & ROWE, D.S. (1972) Immunoglobulin levels and antibody to *Candida albicans* in human cervico-vaginal secretions. *Clinical and Experimental Immunology*, **10**, 427–434.

WARNOCK, D.W. & HILTON, A.L. (1976) Value of the indirect immunofluorescence test in the diagnosis of vaginal candidiasis. *British Journal of Venereal Diseases*, **52**, 187–189.

WARNOCK, D.W., SPELLER, D.C.E., DAY, J.K. & FARRELL, A. (1979a) Resistogram method for differentiation of strains of *Candida albicans*. *Journal of Applied Bacteriology*, **46**, 571–578.

WARNOCK, D.W., SPELLER, D.C.E., MILNE, J.D., HILTON, A.L. & KERSHAW, P.I. (1979b) Epidemiological investigation of patients with vulvovaginal candidosis. *British Journal of Venereal Diseases*, **55**, 357–361.

WILLIAMSON, J.J. (1972a) Diurnal variation of *Candida albicans* counts in saliva. *Australian Dental Journal*, **17**, 54–60.

WILLIAMSON, J.J. (1972b) A study of extent of variation in daily counts of *Candida albicans* in saliva. *Australian Dental Journal*, **17**, 106–109.