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Influence of Antibiotics or Certain Intestinal Bacteria on Orally Administered *Candida albicans* in Germ-Free and Conventional Mice[1]

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Candida albicans, administered by gastric intubation, persisted in the gastrointestinal tract of gnotobiotic mice for long periods but was eliminated within a relatively short period of time in pathogen-free mice. Oxytetracycline administered by mouth had no reproducible effect on the persistence of *C. albicans* in the gastrointestinal tract of either germ-free or pathogen-free mice. Prolonged administration of streptomycin extended the time that *C. albicans* could be recovered from feces of pathogen-free mice when compared to mice not receiving the antibiotic or those receiving a single large dose. There was a brief interval of time during which *C. albicans* could not be recovered from the feces of gnotobiotic mice contaminated with certain intestinal bacteria, but eventually all mice began to shed the fungus again. *C. albicans* administered by mouth was not pathogenic for germ-free or pathogen-free mice. It can be concluded from these findings that mice do not possess an innate resistance to *C. albicans* but that pathogen-free mice do possess some ecological mechanism which prevents establishment of the fungus in their gastrointestinal tract. The reason for the difference in colonization of *C. albicans* in germ-free or gnotobiotic mice and pathogen-free mice was not determined.

Numerous reports indicate that use of antibacterial substances is followed by an increased incidence and severity of candidiasis (26, 27) especially in patients with subnormal host defense. Possible mechanisms allowing antibiotics to increase the hazard of candidiasis have been reviewed (26). Several hypotheses have been advanced to explain the role, if any, of antibiotics in these infections. (i) Antibiotics may directly stimulate the growth of *Candida* or may excite its virulence; (ii) antibiotics may appreciably alter host response to infection or may affect the host tissue by direct drug toxicity or sensitization; (iii) antibiotics may suppress indigenous microflora which under normal circumstances control *Candida* by competition for nutritive substances or by production of substances inhibitory to *Candida*. In addition, other theories hold that candidiasis is not directly related to use of antibiotics per se but is dependent upon certain predisposing factors such as age, state of nutrition, or a debilitating disease with secondary infection by *Candida*.

[1] These studies represent a portion of the dissertation submitted by the author in partial fulfillment of the requirements for the Doctor of Science (Hygiene) degree from Tulane University, New Orleans, La.

In support of the third hypothesis, there is evidence that the intact normal gastrointestinal microflora play a role in the host's defense against enteric infection with several different experimentally administered microorganisms. Treatment with antibiotics to which the experimentally inoculated microorganisms are resistant, but certain of the predominant flora are susceptible, renders the host susceptible to infection (4, 8, 9, 11, 13, 17, 28).

In previous studies, *C. albicans* has been administered to germ-free mice and chickens. Balish and Phillips (2) have shown that oral challenge with *C. albicans* resulted in crop infections in all germ-free chicks, whereas conventional chicks were not infected. They concluded that the enteric microbial flora of the conventional chick provides protection against candidiasis. They further demonstrated that *Escherichia coli* in the intestinal tract of gnotobiotic chicks provides protection against crop infection after oral challenge with *C. albicans*, whereas *Streptococcus faecalis* provides no such protection (3). The same workers (21) and Nishikawa et al. (20) have also shown that *C. albicans* can be established in the intestinal tract of germ-free mice and that the fungus will persist for at least

18 months (in the former report) and for 134 days (in the latter study). Additionally, Nishikawa et al. have shown that gnotobiotic mice monocontaminated with *E. coli* resisted permanent colonization of orally administered *C. albicans*. In contrast though, *Candida* was decreased but persisted for at least 26 days in germ-free mice infected with *C. albicans* and later given *E. coli*.

It was the purpose of the present study (i) to repeat previous work in a single coordinated, controlled study using an experimental model which might give more insight into mechanisms of host resistance and susceptibility (e.g. germ-free versus conventional hosts), and (ii) to include additional aspects not previously considered.

MATERIALS AND METHODS

Organisms and their maintenance. *C. albicans*, strain 374, obtained from G. S. Kobayashi of the Washington University School of Medicine, was maintained by subculture at monthly intervals on Sabouraud dextrose agar (Difco). The virulence of *C. albicans* was tested in conventional mice by intravenous inoculation of washed cells suspended in saline. The LD_{50} at the beginning and end of the study was 10^4 and $10^{4.2}$ viable fungal units, respectively.

Bacteroides sp., *Lactobacillus* sp., *S. faecalis*, and *E. coli* were isolated from feces of pathogen-free mice. *S. lactis* was obtained from a stock culture maintained in this department.

Preparation of inoculum for oral challenge. *C. albicans* was grown in 1% Casamino Acids (Difco)-1% yeast extract (Difco)-2% glucose broth and was incubated at 37 C for 24 hr on a rotary shaker (New Brunswick Scientific Co., New Brunswick, N. J.) operating at about 165 rev/min. The cells were harvested and washed in sterile saline by centrifugation at 400 × *g* for 30 min and resuspended in fresh sterile saline. Total fungal units were determined in a hemacytometer and electronic cell counter (Coulter Counter, model "F," Coulter Electronics, Inc., Hialeah, Fla.), and then cell suspensions were diluted in saline to yield an estimated 10^6 fungal particles in 0.2 ml to inoculate the animals. Viability of particles was demonstrated by plate counts to be approximately 100% at the time of animal inoculation.

Streptococci, *E. coli*, and *Lactobacillus* sp. were grown aerobically in Micro Inoculum broth (Difco). *Bacteroides* sp. was grown anaerobically in a special medium (24). Bacteria were incubated at 37 C for 48 hr.

Animals, inoculation, and maintenance. Male, 20 to 25 g Ham/ICR Swiss mice (CD-1, Charles River Breeding Laboratories, Inc., North Wilmington, Mass.), either pathogen-free or germ-free, were used. They were inoculated by gastric intubation with *C. albicans* at the dosage described above. When specific bacterial contamination was desired, animals were given food over which about 10 ml of a broth culture had been poured.

Gnotobiotic animals and their pathogen-free counterparts were housed in Plexiglas isolators with five or six mice per cage. Gnotobiotic animals were maintained by germ-free techniques. Other mice were housed in stainless steel cages, one or two animals per cage, in a standard animal room environment.

Examination for yeasts. Feces of experimental pathogen-free mice were cultured three times before inoculation to be certain that they did not harbor naturally occurring *C. albicans* in their gastrointestinal tracts. Two fecal pellets from each sample were macerated in 1.0 ml of sterile saline and plated on cyclohexamide agar. As an additional measure, 100 noninoculated, pathogen-free mice were examined to ascertain that animals from the vendor's colony were free of *Candida*. Individual fecal samples from these latter mice were collected daily for 5 days and cultured on cyclohexamide agar and Littman-Oxgall agar (Difco) with added chloramphenicol (Parke, Davis & Co., Detroit, Mich.). Feces of all animals were also cultured on cyclohexamide agar after being inoculated with *C. albicans*; animals were considered free of the fungus after three successive negative cultures. At the termination of each experiment utilizing gnotobiotic animals, the cut surfaces of organs were cultured on cyclohexamide agar.

Examination of gnotobiotic mice contaminated with bacteria. At weekly intervals pooled fecal samples from each group of mice were cultured on all of the media described below. At the termination of each experiment, organs were removed aseptically, and the cut surfaces were cultured on blood agar plates. In addition, samples from the mouth, esophagus, stomach, small intestine, cecum, and colon were also cultured on the following media used for isolation of the various species: Eosin Methylene Blue agar (Difco) for *E. coli*; Lactobacillus selection agar (BBL) or special *Lactobacillus* sp. medium (24); blood agar for streptococci; blood agar with neomycin sulfate (100 μg/ml) or a special medium (24) for *Bacteroides* sp. Plates for isolation of *Bacteroides* sp. and *Lactobacillus* sp. were incubated anaerobically.

Termination of gnotobiotic experiments. At necropsy, the sizes of the ceca of germ-free, gnotobiotic, and pathogen-free mice were compared by gross observation. Tissues were cultured for fungi and bacteria as described above, and portions were placed in 10% buffered Formalin for sectioning. Duplicate sections were stained by hematoxylin and eosin and by the periodic acid-Schiff method.

Antibiotics. Oxytetracycline (Charles Pfizer and Co., Inc., New York, N.Y.) for intravenous administration was added to fresh drinking water daily at a dose of 1 mg/ml. Antibiotic consumption was determined by measuring the amount of solution consumed during each 24-hr period. Drinking water containing antibiotic was available to mice 24 hr before infection with *C. albicans* and for 9 days afterward. The average consumption of oxytetracycline per mouse per day was 4.8 mg. Fifty milligrams of streptomycin sulfate for intramuscular use (Parke, Davis & Co.), diluted in a total volume of 0.2 ml of sterile water, was given to mice by gastric intubation 24 hr before inoculation with *C. albicans*. In one group of mice, streptomycin

was added on each succeeding day for 13 days to fresh drinking water at a dose of 1.0 mg/ml. These latter mice ingested an average of 8.5 mg of streptomycin per day.

RESULTS

Initial experiments were designed to determine the influence of antibiotics upon infections of orally administered *C. albicans* in germ-free or pathogen-free mice, or both. It was shown that *C. albicans* could not be permanently established in the gut of pathogen-free mice, but it could be readily established and maintained in germ-free mice (Fig. 1A and B). The fungus could no longer be recovered from pathogen-free mice by 32 days after inoculation. In a few instances, some of these mice were fungus-free within 24 hr after inoculation. However, gnotobiotic mice retained the fungus through the experimental period (up to 152 days after inoculation). Oxytetracycline did not have any reproducible effect on the establishment of the fungus in mice (Fig. 1A and B). In one group of pathogen-free mice, fecal excretion of *C. albicans* persisted longer in mice receiving the antibiotic than in mice not receiving it. However, when the experiment was repeated, this order was reversed. In germ-free mice orally inoculated with *C. albicans*, oxytetracycline administration for 10 days did not appear to have any influence on the fecal excretion of the fungus by the mice. At necropsy, *C. albicans* was not isolated from the gastrointestinal contents of pathogen-free mice but was recovered from the digestive tract of all gnotobiotic mice.

Another experiment was set up to determine whether reducing the gram-negative enteric flora by administration of streptomycin would influence the establishment of *C. albicans* in the gut of pathogen-free mice. These animals were housed in a standard animal room environment. As shown in Fig. 2, prolonged administration of streptomycin extended the time that *C. albicans* could be recovered from feces of pathogen-free mice when compared to mice not receiving the antibiotic or those receiving a single large dose.

Finally, experiments were designed to ascertain whether contamination of germ-free mice with certain enteric bacteria before or after inoculation of *C. albicans* would influence the establishment of the fungus in the gut. In one experiment, four groups of germ-free mice (five or six per group) were treated as follows: group 1, *E. coli* followed by *C. albicans* 13 days later; group 2, *C. albicans* only; group 3, *E. coli* only; and group 4, saline only. Mice in groups 2 and 4 were contaminated also with *E. coli* 64 days after the time that mice in group 2 were given *C. albicans*. All animals were held 133 days from the time groups 1 and 2 were given *C. albicans*.

E. coli was readily established in the gastrointestinal tract of the germ-free mice. Germ-

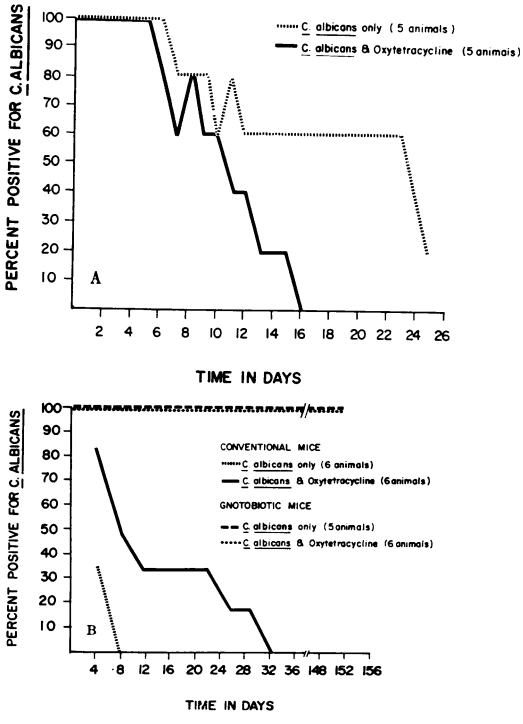

FIG. 1. *Persistence of Candida albicans in the gastrointestinal tract, determined by fecal culture, of mice after oral inoculation of 10^6 fungal units and addition of oxytetracycline to the drinking water at a dose of 1 mg/ml for 10 days beginning 1 day before inoculation with the fungus. A, Pathogen-free mice maintained in a standard animal room environment; B, pathogen-free and gnotobiotic mice maintained in an isolator.*

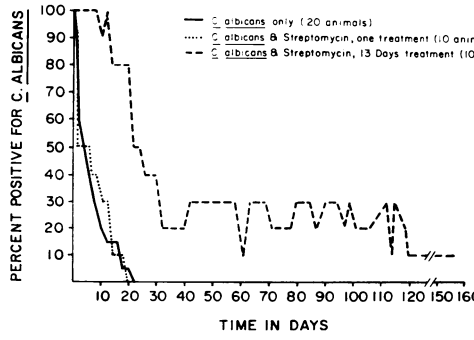

FIG. 2. *Persistence of Candida albicans in the gastrointestinal tract, determined by fecal culture, of pathogen-free mice after oral inoculation of 10^6 fungal units and treatment with streptomycin.*

free animals monocontaminated with *C. albicans* shed the fungus more abundantly than mice with a diflora of *E. coli* and *C. albicans*. This was true whether *E. coli* was administered before or after inoculation with *C. albicans*. Mice with a diflora of *E. coli* and *C. albicans* continued to shed *C. albicans* in the feces for 133 days after inoculation with the fungus, at which time the experiment was terminated. At necropsy, *C. albicans* and *E. coli* were recovered from the digestive tract of all inoculated mice.

In another experiment, 10 germ-free mice were contaminated with *Lactobacillus* sp. and *S. lactis*; *Bacteroides* sp.; and *E. coli* and *S. faecalis*, on days 1, 11, and 20, respectively. *C. albicans* was administered on day 40. After contamination with *Bacteroides* sp., some mice became ill and developed diarrhea, and five of them died. Therefore, the following protocol was adopted. Six mice were given the five bacteria and *C. albicans*, five mice were inoculated with *C. albicans* only, and five mice were maintained as germ-free controls. All mice were held 84 days after inoculation with *C. albicans*.

In mice given the five bacteria and *C. albicans*, all organisms were established in the gut; however, there was an interim period when fungus could not be recovered (Fig. 3). In gnotobiotic mice contaminated with bacteria, *C. albicans* was recovered from feces of two animals 3 days after inoculation with the fungus but was not recovered from any at 10 days. However, by 31 days after inoculation, all mice were shedding the fungus and continued to do so until they were killed at

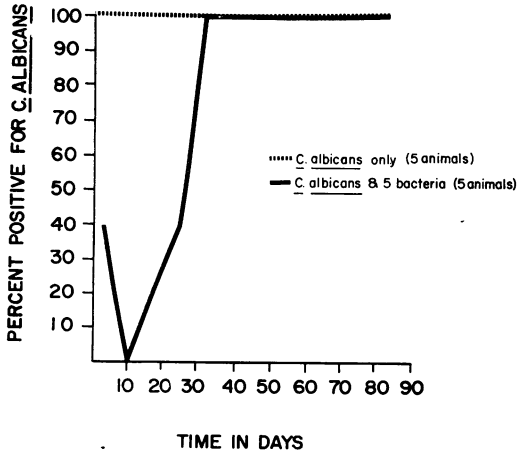

FIG. 3. *Persistence of Candida albicans in the gastrointestinal tract, determined by fecal culture, of gnotobiotic mice after oral inoculation of 10^6 fungal units. One group of mice was contaminated with Lactobacillus sp., Escherichia coli, Bacteroides sp., Streptococcus lactis, and S. faecalis before inoculation with the fungus.*

84 days postinoculation. At necropsy, all five bacteria and *C. albicans* were recovered from the contents of the digestive tract of each contaminated animal.

No gross or histological lesions associated with *C. albicans* were observed, nor was the fungus recovered from brain, heart, lungs, kidney, liver, spleen, or pancreas of inoculated mice. When compared to pathogen-free mice, the ceca of germ-free animals were considerably enlarged, and monocontamination with *C. albicans* did not appear to decrease the size. Monocontamination with *E. coli* caused a slight reduction in size. However, when five enteric bacteria were given to germ-free mice, the size was reduced approximately fourfold, but even so, ceca were about twice the size of those from pathogen-free mice. The fungus dia not produce evidence of clinical disease in any animal.

Results from control mice (not inoculated with *C. albicans*) in all experiments were unremarkable. Fecal culture of uninoculated, pathogen-free mice never revealed *Candida*, but *Geotrichum* sp. and *Rhodotorula* sp. were isolated.

DISCUSSION

The work reported herein shows that pathogen-free mice resist permanent colonization with *C. albicans* administered orally, whereas similarly inoculated germ-free or gnotobiotic mice become colonized. Thus, it can be concluded that mice do not possess an innate resistance to *C. albicans*, but it is equally apparent that pathogen-free mice do possess some ecological mechanism which prevents establishment of the fungus in their gastrointestinal tracts. The reason for the difference in colonization of *C. albicans* in the two types of mice was not deducible from the present study. Neither did this study suggest an explanation for the difference in rate of elimination of the fungus that was observed among individual pathogen-free mice.

Some facets of the mechanism of host resistance and susceptibility and the relation of antibiotics in *Candida* infection have been explored. This study repeats some previous work, but includes additional aspects not previously considered: (i) administration of oxytetracycline to gnotobiotic mice experimentally infected with *C. albicans*; (ii) longer periods of observation of experimentally infected animals which might more closely parallel events in natural human infections; (iii) contamination of germ-free mice with five enteric bacteria, namely, *Bacteroides* sp., *Lactobacillus* sp., *S. faecalis*, *E. coli*, and *S. lactis*, with subsequent inoculation of *C. albicans*.

The observation that *C. albicans* cannot be permanently established in conventional mice

agrees with some prior reports (13, 20, 22, 28). Huppert, Cazin, and Smith (13) found that most conventional mice given a single oral inoculum of *C. albicans* eliminated the fungus by 48 hr. Sternberg et al. (28) found that conventional mice completely eliminated even three gastric dosings of *C. albicans* given on consecutive days, and after the final dose there was a continual daily reduction in the number of fungal cells in the feces, although a few mice maintained the organisms for more than 90 days. Rao and Sirsi (22) noted that large inocula (1.8×10^8) of *C. albicans* by the oral route could not cause any dissemination of the fungus from the gastrointestinal tract or facilitate the multiplication of the organism in a healthy mouse. However, it is not clear from their results when, or if, the gastrointestinal tract became free of the fungus.

Other workers (21), however, reported that infected conventional mice maintained *C. albicans* in their gut flora after oral inoculation, but the mice were observed for only 21 days. At necropsy, the colony counts of *C. albicans* taken on contents from the small intestine of mice were about 10^6 per g (wet weight).

The observation regarding the persistence of *C. albicans* in mice that were initially germ-free is in agreement with the reports of other investigators. In the experiments reported herein, germ-free mice which were orally inoculated with *C. albicans* were held for as long as 152 days, and this fungus was recoverable from the gastrointestinal tract during this entire time. Similarly, Phillips and Balish (21) and Nishikawa et al. (20) found that animals monocontaminated with *C. albicans* remained colonized at least 18 months and 134 days, respectively.

In addition, the observation that *C. albicans* could not be isolated from feces of normal conventional mice agrees with findings of others (13, 14, 21, 28).

Antibiotics seem to vary in ability to influence the establishment of *C. albicans* in gut flora. In the present experiments, oxytetracycline did not have a consistent influence in either germ-free or pathogen-free mice. Huppert et al. (13), however, found that oxytetracycline administered orally predisposed consistently toward the establishment of *C. albicans* in the microbial flora of the intestinal tract of mice. Their findings were based on fecal cultures taken 48 and 72 hr after inoculation of the fungus. In criticism of the work of Huppert et al., it should be stated that 2 or 3 days is probably too brief a time to determine establishment of an organism within the gastrointestinal tract, because the studies presently reported showed that *C. albicans* can be recovered from the gastrointestinal tract of some conventional mice after 48 to 72 hr but that the organism is not permanently established. In experiments of Sternberg et al. (28), in which the drug was also given orally, oxytetracycline again seemed to favor the harborage of *C. albicans* in the gut but only when the oral inoculum of the yeast was high (e.g. 6×10^7).

Several investigators have shown that oral administration of streptomycin increases the infectivity of certain orally administered bacteria in mice (4, 11, 17, 18), but the published evidence regarding the effect of streptomycin on *Candida* susceptibility is not nearly so convincing. Huppert et al. (13) found that orally administered dihydrostreptomycin predisposed to establishment of *C. albicans* in the gut flora after oral inoculation. In their experiments, more treated mice had positive stool cultures at 48 and 72 hr after oral inoculation of *C. albicans* than nontreated mice. However, as stated previously, observations for such a brief period of time cannot be reliably interpreted. In the current study, repeated streptomycin treatment prolonged the persistence of *C. albicans* in some mice although eventually most individuals eliminated the yeast, irrespective of streptomycin treatment.

A number of investigators have presented evidence of the competitive interaction between bacteria in vivo. Bohnhoff, Miller, and Martin (5) found that two fatty acids, acetic and butyric, recovered from the bowel content of nontreated mice, and also from cultures of *Bacteroides*, inhibited the multiplication of *S. enteritidis* in vitro. They concluded (6), therefore, that inhibition of this bacterium in the colon content of mice is determined by *p*H and by the concentration of acetic, butyric, and lactic acids. Meynell (16) determined that the joint effects of a low E_h and short-chain volatile fatty acids account for the failure of orally inoculated *Salmonella* to increase in the normal mouse gut. Freter (12) suggested that the dominant inhibitory mechanism in the mouse gut is competition between microorganisms for fermentable carbon sources in a reduced medium. Abrams and Bishop (1) think that the normal flora does not influence mucosal resistance directly, but contributes to the control of *S. typhimurium* in the small intestine primarily by stimulating peristaltic emptying.

The effects of dead or live bacteria or extracts on infections with *C. albicans* have been studied. Dobias (7) has stated that some infections in mice were enhanced when certain live or dead gram-negative bacteria, including *E. coli* or the products therefrom, were administered simultaneously or shortly after *C. albicans*. He hypothesized that during antibiotic therapy, destruction of large

numbers of gram-negative, endotoxin-producing bacteria of the normal gastrointestinal flora may cause sudden liberation of large amounts of endotoxin which predispose the host to *C. albicans* infections. He contended that antibiotics would not enhance the growth of *Candida* in animals which are otherwise free from microorganisms. In support of this contention, oxytetracycline did not predispose to *Candida* infection in gnotobiotic mice in the studies reported herein. Balish and Phillips (2) demonstrated that oral challenge with *C. albicans* resulted in crop infections in all germ-free chicks but no such infections in conventional chicks. These investigators concluded that the intestinal flora of the conventional chick provides protection against candidiasis of the digestive tract and that the protection observed was due to bacterial inhibition of hyphal development in *C. albicans*. Evidence was given that *E. coli* in the intestinal tract of gnotobiotic chickens provides protection against crop infection after oral challenge with *C. albicans*, whereas *S. faecalis* provides no such protection (3).

If competition between the intestinal microflora and *C. albicans* is responsible for the failure of this fungus to be established in the gut of conventional mice, then contamination of germ-free mice with bacteria from conventional mice should simulate conditions in the conventional animal with comparable results. However, this necessitates knowledge of the composition of the mouse gastrointestinal microflora. Studies related to this subject have been accomplished (8, 9, 10, 23, 24, 25). In the work reported herein, *E. coli*, alone or with *Bacteroides* sp., *Lactobacillus* sp., *S. lactis*, and *S. faecalis*, did not simulate in germ-free mice the conditions which in pathogen-free mice prevented the long-term establishment of *C. albicans* in the gastrointestinal tract. During the first few days after inoculation with *C. albicans*, yeast was being shed from some of the mice, but by the tenth day it was no longer recoverable from the feces of any of the mice contaminated with the five bacteria. The following week, however, *C. albicans* was isolated from one mouse; at 2 weeks, two mice were positive; and after 3 weeks, all mice, surprisingly, were again positive (Fig. 3). The reasons for this finding are not apparent from the results of this study.

In germ-free mice first contaminated with *E. coli* and later given *C. albicans*, Nishikawa et al. (20) reported, contrary to findings reported herein, that *C. albicans* was not established in the gut. However, in germ-free mice in which the order of contamination of the organisms was reversed, i.e., *C. albicans* first and *E. coli* second, both were established and persisted for at least 26 days, when the experiment was terminated. This latter finding agrees with the work presently reported.

Additional studies including quantitative methods are needed to elucidate the antagonism to *C. albicans* in the gastrointestinal tract of conventional mice. It is suggested that fusiform bacteria may play a role since others (23) have shown that they appear to be the dominant bacteria in certain portions of the digestive tract. However, physiological, biochemical, anatomical, or even immunological factors could be involved. In support of this, it has been observed by others (15) and also noted in the present study that germ-free and certain gnotobiotic animals have enlarged ceca, and it may be that this extra capacity of the gastrointestinal tract serves as a reservoir for *Candida*. Furthermore, Dubos et al. (8, 9) reported that peristalsis is slower in germ-free animals, and Abrams and Bishop (1), in comparing *S. typhimurium* infection in germ-free and conventional mice, concluded that the conventional flora contributes to the control of the population of this bacterium in the small intestine primarily by stimulating peristaltic emptying. Therefore, slower peristaltic movement in germ-free and gnotobiotic mice could account at least in part for the persistence of *C. albicans*. Grossly, contamination of germ-free mice with bacteria did not completely reduce the size of the ceca to that of pathogen-free mice in the present series of experiments.

The studies reported herein do show that orally administered *C. albicans* does not invade the gastrointestinal tract or other organs of pathogen-free or of gnotobiotic mice. Other work (19, 21) supports this contention, although Phillips and Balish (21) did find that *C. albicans* invaded the stomach mucosa of one strain of monocontaminated gnotobiotic mice.

An experimental model for the study of candidiasis is needed in which the disease could be produced in a similar manner as in man, namely from the gastrointestinal tract. Mourad and Friedman (19) have pointed out that laboratory studies of candidiasis have been hampered by the inability to produce consistently a prolonged infection in laboratory animals. Most previous animal studies show the pathological changes produced either in conventional animals by massive doses of *C. albicans* administered by a parenteral route (7, 19, 27) or in modified hosts (19), but neither simulates accurately the process taking place in human candidiasis. Also, animals given *Candida* orally could not be colonized regularly. Observations in the present study indicate that the gnotobiotic mouse is a useful experi-

mental model for candidiasis inasmuch as the germ-free or the gnotobiotic mouse contaminated with certain bacteria can regularly be colonized with *Candida* and may possibly maintain the fungus in the gastrointestinal tract for its lifetime. In such a host, the effect of hormones, antibiotics, antineoplastic agents, other microorganisms or their products, and numerous other agents and factors could be studied as they relate to enhancement of candidiasis. Also, if one could determine the mechanism whereby conventional mice are resistant to long-term colonization with *C. albicans*, a new insight into the pathogenesis of candidiasis in both men and animals could result.

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