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Dominant Mutation for Nystatin Resistance in Yeast

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In general, attempts to isolate strains of *Candida albicans* resistant to the commonly employed antifungicide nystatin have been unsuccessful (M. L. Littman, M. A. Pisano, and R. M. Lancaser, Antibiotics Ann. 1957–58, p. 981, 1958; C. K. J. Paniker, P. V. Kurup, and K. Indira Devi, Indian J. Med. Res. **51**:846, 1963). A few strains, however, have yielded variants exhibiting three- to fourfold resistance (H. A. Stout and J. F. Pagano, Antibiotics Ann. 1955–56, p. 704, 1956; P. V. Forni, Giorn. Bacteriol. Immunol. **51**:149, 1958). In addition, the isolation of nystatin-resistant mutants of *Saccharomyces cerevisiae* has been reported (K. A. Ahmed and R. A. Woods, Genet. Res. **9**:179, 1967).

From a strain of *C. albicans*, isolated from a case of vaginitis and normally killed by concentrations of nystatin over 20 units/ml, we were able to isolate variants resistant to 80 units/ml with relative ease. These appeared at a frequency of approximately 10^{-7} when 10^8 cells were spread on agar containing 80 units of nystatin per ml, and most remained stable throughout several transfers in the absence of nystatin. Figure 1 shows survival curves for the parent strain and one of the resistant variants. An additional 50 strains, which had been isolated from patients, were typed and all proved to be *C. albicans*.

Because of the lack of a method of genetic analysis in *Candida* species, we turned to laboratory stocks of *Saccharomyces* to investigate the genetic basis of nystatin resistance in yeast. Stable resistant variants of three haploid strains were again isolated without difficulty. These showed tolerances towards nystatin of up to 12-fold those of the original strains. Twelve of the variants were crossed with nystatin-susceptible haploid strains of opposite mating type; in each case, the resulting hybrids, upon sporulation, produced two resistant and two susceptible spores per ascus (Fig. 2). Thus, the basis of resistance in each variant is mutation of a single gene. These results are similar to those obtained by Ahmed and Wood (Genet. Res. **9**:179, 1967).

Our results, however, also show an important difference from those of the latter. In only 1 of the 12 mutants was the mutation for resistance recessive to wild type (susceptibility). In eight mutants, resistance was fully dominant (Fig. 2). Hybrids between sensitive strains and the remaining three mutants showed intermediate phenotypes with degrees of resistance approximately midway between the parent strains.

These mutants have not yet been tested for allelism, so we do not know whether one or more dominant genes are involved. The existence of at least one dominant gene for resistance to nystatin could, however, be of considerable importance. Unlike recessives, dominant genes are expressed regardless of ploidy and of the other alleles present. Thus, unless strains of *C. albicans* are generally haploid, dominant genes for resistance would be of greater significance than recessive mutations in the treatment of moniliasis with nystatin.

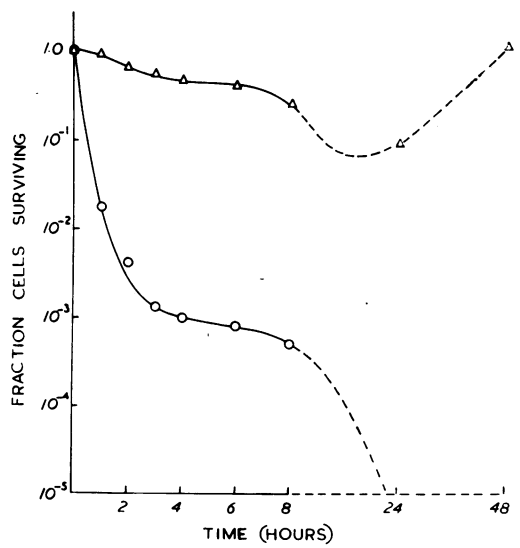

FIG. 1. *Survival curves for 80 units/ml concentration of nystatin. Symbols;* ○, *parent strain of Candida albicans;* △, *mutant of this strain resistant to 80 units/ml. (The result for the parent strain at 24 hr was 0 colonies from 2* × 10^5 *cells plated.)*

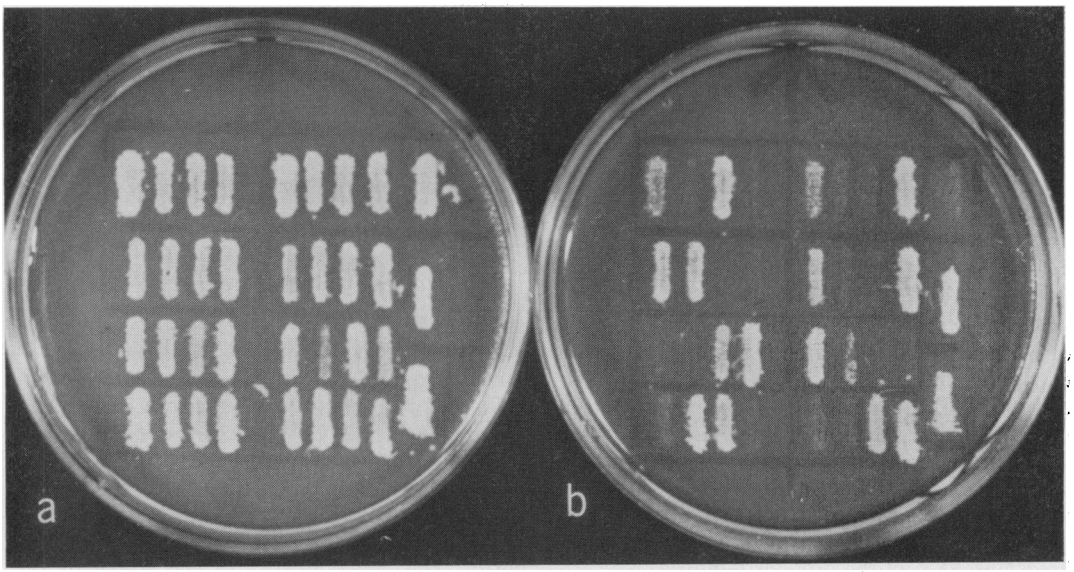

FIG. 2. *Two replica plates of streaks from eight tetrads of a Saccharomyces hybrid of wild type (nystatin-susceptible) with a dominant mutant resistant to a 10-fold concentration of nystatin. The three streaks running vertically at the extreme right of the plates are (top to bottom) wild-type parent, mutant parent, and hybrid. (a) Control (without nystatin), (b) nystatin-agar.*