of these strains was retested but showed no change in degree of sensitivity to the drug *in vitro*. Six recurring infections were treated with second courses, and five cleared.

One of these patients, receiving 1½ million units a day, developed nausea and vomiting on the sixth and seventh days of her course. Several others complained of slight nausea at about the same stage, and three of the earlier patients, who were receiving a suspension of the powdered drug, complained of its offensive taste, but this difficulty did not arise when compressed chocolate-covered tablets were given. No other toxic symptoms or signs were noted. In concentrations of 30 units per ml., nystatin did not interfere with the phagocytic properties of human leucocytes when incubated at 37° C. with suspensions of cells prepared from buffy coat or cerebrospinal fluid.

Discussion

These results show that nystatin inhibits cell-division and mycelial growth of candida and saccharomyces, including pathogenic strains isolated from a variety of human lesions. This effect, detectable at unit strength against an assay organism, is fairly complete against *C. albicans* at concentrations of 5–20 units per ml.

Any assessment of the efficacy of nystatin against pharyngo-respiratory mycotic infections must be based upon a critical realization of the superficial nature and tendency to spontaneous amelioration of many monilial lesions. Establishment and colonization, in the first place, probably depend upon devitalization of the epithelium and alterations in the pharyngeal flora, and can be provoked by antibacterial therapy. Withdrawal of the responsible antibacterial drug often allows such mycotic superinfection to disappear. When colonization occurs—as evidenced by fungal growth around desquamated epithelial plaques in film preparations—it may persist in the presence of a mixed bacterial flora. A number of other factors—including dentures, atrophic mucosae in older people, poor nutritional states, uraemic and other toxic conditions, and the prevalence of pathogenic candida in the environment—all contribute to the initiation and intensity of the infection. These factors not infrequently combine to render moniliasis an awkward therapeutic problem. From the results now available it can be claimed that nystatin is an agent of very definite promise in this field. Its specificity of action against fungi, its lack of interference with antibacterial agents, and its apparent lack of toxicity would appear to be unique properties.

A clue to the mechanism of action may be present in the antagonisms and additive effects obtainable with various carbohydrate substances. The presence of a chain of CH_2 groups, as in the alcohols, favours activity, while CHOH and CHO groups, as in various sugars, are antagonistic. Glycols, with combination of both, show intermediate properties. These results may also explain in part some variations observed in prophylactic and therapeutic trials, in that the circulating level of blood glucose, and possibly substances present in exudates, could theoretically interfere with the action of low concentrations of nystatin. At its best this action is fungistatic, so that, in the absence of local tissue immunity or re-establishment of a competitive flora, recrudescence of candida infection could be expected to follow cessation of treatment.

The experiments with higher alcohols described above suggest that a more complete effect might be obtainable by adding these to topical forms of nystatin.

Exposure of candida and saccharomyces to subinhibitory and fully inhibitory concentrations of nystatin *in vitro* disclosed no tendency on the part of the surviving organisms to acquire resistance. Likewise, reassay of strains re-isolated after treatment revealed no change in sensitivity. Since the mechanisms by which micro-organisms acquire resistance are many and varied, these limited results are far from conclusive, but they suggest that rapidly developing acquired resistance, of the type found with streptomycin, does not readily affect organisms exposed to nystatin.

Its action upon the growth and division of candida, together with therapeutic results obtained to date, suggests that nystatin is worthy of extended trial in patients with established mycotic infections. There is, however, no justification at present for its use prophylactically.

Summary

"Nystatin" ("mycostatin"), an antibiotic substance derived from *Streptomyces noursei*, inhibits the growth and cell division of species of candida and saccharomyces.

In its mode of action this substance is complex but highly specific. Activity is favoured by CH_2 chains and antagonized by CHOH. Bacteria and human leucocytes are not affected by concentrations which are highly toxic to fungal cells.

A therapeutic trial in 22 patients with simple mycotic infections, mainly with *C. albicans*, showed rapid and complete clearance of infection in 16 and temporary clearance in 4. Apart from transient nausea, no toxic effects were observed.

Nystatin and antibacterial agents showed no mutual interference *in vitro*, but when given prophylactically nystatin was not wholly successful in preventing mycotic superinfection in patients receiving antibacterial therapy. Resistance to nystatin was not found in strains after passage *in vitro* or on re-isolation during and after treatment.

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EFFECT OF NYSTATIN ON GROWTH OF CANDIDA ALBICANS DURING ANTIBIOTIC THERAPY

BY

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The disturbing effect of the broad-spectrum antibiotics on the normal microflora of the host receiving them is one of the most important and potentially dangerous aspects of their use. Several observers have drawn attention to the increased frequency with which *Candida albicans* colonizes such regions as the mouth and bowel (Sharp, 1954; Cannon, 1955; Loh and Baker, 1955; Carpenter, 1955). The present investigation was carried out to see if the simultaneous administration of an antimycotic drug "nystatin" ("mycostatin") to patients who were receiving tetracycline would have any effect upon the overgrowth of *C. albicans*. Nystatin is derived from cultures of *Streptomyces noursei*, and is described as a pale, almost colourless, crystalline substance (Hazen and Brown, 1950). *In vitro* it is reported to be most

effective in suppressing yeast-like fungi which are in the growing stage, and to be less active against spores. It is inactive against bacteria (Tarbet, Oura, and Sternberg, 1953).

Method of Investigation

The patients studied were 50 males aged over 12 years, admitted to Ruchill Hospital, between June and November, 1955, with the diagnostic label of pneumonia. They had not been treated by adequate chemotherapy prior to admission. There was no selection of patients; they were allocated alternately to treatment either with tetracycline alone or with tetracycline + nystatin.

The patients who received tetracycline only (Group A) were given the antibiotic orally in a dosage of 0.25 g. four-hourly for 48 hours, after which the dose was reduced to 0.25 g. six-hourly for a further three days. They thus received a total dose of 6 g. of tetracycline in five days. In the tetracycline + nystatin group (Group B) tetracycline was given in the same dose as in Group A. In addition, nystatin was administered orally, the dose given being one tablet eight-hourly. Each tablet contained 500,000 units of nystatin. (A unit of nystatin is defined as the amount that completely inhibits growth of *C. albicans* in 1 ml. of broth.)

On admission, and before treatment was begun, a rectal swab, a throat swab, and a specimen of sputum were taken from each patient. Further rectal and throat swabs and specimens of sputum were obtained on the third, fifth, seventh, and ninth days in hospital. The swabs and the sputum (which was collected in a sterile glass container) were inoculated direct on to Sabouraud's medium, and the plates incubated at 37° C. The plates were examined for growth of yeasts after 48 hours. All plates which showed no growth at this stage were kept for a further 14 days at bench temperature before being finally discarded as negative. The growth of *C. albicans* was recorded as being "absent," "scanty," or "heavy." *C. albicans* was identified by its colonial and microscopical appearances and by fermentation reactions.

The colonies on Sabouraud's medium are large, smooth, white, or cream-coloured, lustreless, 2–4 mm. in diameter, and have the ability to grow at room temperature. Microscopically, yeast cells are seen in colonies from Sabouraud's plates, and the typical mycelial form appears when grown on corn-meal agar. The fermentation reactions have been studied with some of the strains with somewhat variable results. In general, acid and gas were produced when grown in glucose and maltose, and acid only in sucrose. It is hoped to study this aspect in greater detail.

Results

1. *Admission Specimens.*—Examination of admission specimens showed that *C. albicans* was present in 26% of all rectal swabs, 24% of all throat swabs, and 38% of all sputa (Table I). Heavy growths were obtained in 8% of rectal swabs, 10% of throat swabs, and 16% of sputum specimens. The patients' ages ranged from 12 to 81 years. There were 14 aged under 40, and 36 aged 40 and over; and the average age was 46. Of the 50 cases in the series, 19 gave a history of chronic respiratory disease (38%), and 18 of these were over the age of 40 years. The presence of *C. albicans* in the sputum was correlated with the age group and with the presence or absence of chronic respiratory disease; the results are shown in Table II. It would seem that the presence of *C. albicans* in the sputum is not related to either of these characteristics. These figures are very similar to those reported by Sharp (1954).

2. *Specimens Examined During Treatment.*—The results of the subsequent examination of these patients are shown in Table III.

(*a*) *Rectal Swabs.*—The number of specimens in Group A (tetracycline only) in which a growth of *C. albicans* was present was 7 (28%) on the day of admission. This figure rose to 13 (52%) on the fifth day (the day on which treatment was discontinued) and to 16 (64%) on the ninth day. It will be noted that heavy growths were obtained from 2 cases on admission, from 10 on the fifth day, and from 11 on the ninth day. In Group B (tetracycline+nystatin) the number of specimens in which *C. albicans* was found to be present was 6 (24%) on the day of admission, 5 (20%) on the fifth day, and 6 (24%) on the ninth day. Heavy growths were obtained from 2 cases on admission, from 1 case on the fifth day, and from none on the ninth day.

(*b*) *Throat Swabs.*—In Group A the number of specimens from which a growth of *C. albicans* was obtained was 5 (20%) on admission, a figure which rose to 13 (52%) on the fifth day and to 14 (56%) on the ninth day. Of these, heavy growths were obtained in 2, 7, and 6 patients respectively. In Group B

TABLE I.—*All Admission Specimens*

Growth of *C. albicans*	Rectal Swab	Throat Swab	Sputum
Absent ..	37 (74%)	38 (76%)	31 (62%)
Scanty ..	9 (18%)	7 (14%)	11 (22%)
Heavy ..	4 (8%)	5 (10%)	8 (16%)

TABLE II.—*Incidence of C. albicans in Admission Sputa in Relation to Age and Chronic Respiratory Disease*

Section	No. of Patients	*C. albicans* Present	Heavy Growth *C. albicans* Present
Aged less than 40	14	6 (43%)	3 (21%)
Aged more than 40	36	13 (36%)	5 (14%)
With chronic respiratory disease	19	7 (37%)	2 (11%)
No chronic respiratory disease ..	31	12 (39%)	6 (19%)
Whole series	50	19 (38%)	8 (16%)

TABLE III.—*Specimens Taken During and After Treatment*

Day of Examination	Treatment Group*	Rectal Swab			Throat Swab			Sputum		
		Ab	S	H	Ab	S	H	Ab	S	H
On admission	A	18	5	2	20	3	2	18	3	4
	B	19	4	2	18	4	3	13	8	4
3	A	17	4	4	16	5	4	..	..	..
	B	20	5	0	19	3	3	..	..	..
5	A	12	3	10	12	6	7	10	7	8 †
	B	20	4	1	17	4	4	11	8	6 †
7	A	6	5	14	10	8	7	..	..	..
	B	24	1	0	15	6	4	..	..	..
9	A	9	5	11	11	8	6	6	11	8 ‡
	B	19	6	0	17	4	4	9	9	7 ‡

* Group A treated with tetracycline only, Group B with tetracycline and nystatin. Ab=Absent. S=Scanty. H=Heavy. † 3rd to 5th day. ‡ 7th to 9th day.

C. albicans was isolated from 7 (28%) on admission, 8 (32%) on the fifth day, and 8 (32%) on the ninth day. The heavy growths were 3, 4, and 4 respectively.

(*c*) *Sputum.*—In Group A *C. albicans* was present in 7 (28%) of the admission specimens, 15 (60%) of the specimens taken on the third to the fifth days, and 19 (76%) of the specimens taken on the seventh to the ninth days, and of these the heavy growths were 4, 8, and 8 respectively. In Group B growths of *C. albicans* were present in 12 (48%) of the admission specimens, 14 (56%) on the third to the fifth days, and 16 (64%) on the seventh to the ninth days. Heavy growths were 4, 6, and 7 respectively.

Clinical Effects.—Side-effects of treatment were as follows. In four cases diarrhoea occurred about four days after treatment had stopped and persisted for about one week. All four were in Group A. In three of them heavy growths of *C. albicans* were obtained from the rectal swabs. No patients developed diarrhoea or other side-effects in the group given combined treatment.

Discussion

It is apparent that a large proportion of the admission specimens from Glasgow patients with pneumonia are found to contain *C. albicans*. The sputum yielded positive results more frequently than rectal or throat swabs. Our results with sputum are similar to those obtained by Sharp (1954), but it seems possible that variations in rates may be encountered between different geographical areas, for

Schwarting and Skinner (1949) isolated the fungus from only 20% of 500 patients admitted to a tuberculosis sanatorium in the United States.

Treatment with tetracycline caused an increase in the number of specimens from which *C. albicans* could be isolated. In the present series there was a gradual rise up to the seventh day in hospital—that is, two days after treatment was discontinued. This increase was observed in all the regions examined.

When nystatin was added to the tetracycline the culture results were not uniform although there seemed to be a tendency towards lower yields. Thus the results of examination of rectal swabs seemed to indicate a definite trend towards the elimination of heavy growths. The effect upon the throat was less obvious, although no marked rise occurred. So far as the sputum was concerned the two treatment groups seemed to be similar.

Nystatin would thus appear to be most effective in the bowel, less effective in the throat, and without effect in the sputum. The apparent effectiveness of the material in the bowel would be in keeping with a suggestion that a high local concentration of antibiotic is important in achieving an antifungal action *in vivo*. The manufacturers state that the absorption of nystatin from the bowel is poor and that negligible amounts appear in the blood. If this is the case the inability of nystatin to control the increase of *C. albicans* in the sputum is understandable, but leaves its moderate effect in the throat to be explained. That this is in no way due to local action is certain, for although the drug is taken orally the antibiotic is contained in pills which are sugar-coated and are swallowed entire. The question of absorption obviously deserves further scrutiny.

The importance of overgrowth of candida in the bowel still awaits proper appraisal. It would seem, however, to be of less clinical significance than systemic infection, which is at least potentially dangerous. The results of the present study would seem to indicate that the oral administration of nystatin would be unlikely to control candida infection in sites which could be reached only by the blood stream.

Summary

The frequency with which *Candida albicans* occurred in throat swabs, rectal swabs, and sputum from 50 patients with pneumonia was observed before, during, and after treatment with either tetracycline alone or tetracycline combined with a new antimycotic drug, nystatin. Nystatin seemed to be effective in reducing the number of patients from whom heavy growths of candida were obtained from rectal swabs. A convincing effect upon the yield of the fungus from the throat and from the sputum was not apparent. These results are in keeping with a view that nystatin does not appear in the blood stream in adequate concentration and that the antibiotic might be ineffective in the treatment of systemic infection.

I wish to thank Dr. T. Anderson, Reader in Infectious Diseases at Glasgow University, for his help in preparing this paper. I am also indebted to Messrs. Squibb for the supply of the drugs used.

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There is now a record total of 26,895 pharmaceutical chemists in Great Britain, states the registrar's report to the Pharmaceutical Society, an increase of 331 in twelve months.

EARLY SIGNS OF BLADDER-NECK DISEASE*

BY

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Certain data are here presented to emphasize what a large part chronic inflammation plays in the aetiology of bladder-neck disease, which may or may not lead to some degree of urinary obstruction.

My interest in this subject has been sharpened because in removing bladder-neck obstructions by open operation from 500 cases I found that 31% were clinically fibrous obstructions—that is to say, of the type which would be wrongly treated by attempted enucleation. I believe the incidence to be greater than this, because I have not included those cases which were treated by endoscopic resection. The method of diagnosis was threefold, and was carried out on the operating table at the time of the removal of the obstruction. The routine adopted was cystoscopy, rectal palpation, and combined inspection and palpation of the internal urinary meatus through the open bladder. The cases of endoscopic resection were excluded because of the lack of opportunity of examining the internal meatus through the open bladder.

Because fibrosis was so commonly encountered, Dr. Robert Thomson, pathologist of St. Peter's, St. Paul's, and St. Philip's Hospitals, made a careful histological search for signs of inflammation of the obstructing tissue removed by me from 50 consecutive cases. He found them in all cases, including those of adenomatous prostates removed by enucleation. I might add that as I do not use indwelling catheter drainage pre-operatively in removing obstructions the inflammation found cannot be attributed to such a cause. So far as I am able to discover, Marion in 1912 was the first to point out that chronic prostatitis and fibrosis of the prostate resulted from any type of urethritis (Marion, 1940).

In 1850 Civale put forward the theory that the bulk of the cases of chronic retention without prostatic enlargement were due to primary atony of the bladder. But now that fibrous bladder-neck obstruction is commonly recognized we no longer see cases of primary atony of the bladder. But by no means all cases can be fitted into the Marion category; indeed, we recognize another group in young adults of both sexes in whom disturbances of micturition develop insidiously and show inflammatory changes in the posterior urethra.

The commonest disturbance of micturition from these changes is chronic increased frequency of micturition; but this symptom is to be found in both sexes at all ages. Therefore I have taken a consecutive series of cases of men, women, and children with chronic increased frequency of micturition and examined them with urethroscope, cystoscope, and in other ways where necessary. There were 274 cases in all. Lesions in the posterior urethra recognizable as inflammatory (including hillocks) were noted in 88%.

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