

TREATMENT OF MONILIAL VAGINITIS

A CLINICAL TRIAL OF NYSTATIN

BY

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Since the preparation of the antifungal antibiotic nystatin from *Streptomyces noursei* by Hazen and Brown in 1950, there have been reports of its use in the prevention of experimental infections with candida (monilia) in animals (Brown, Hazen, and Mason, 1953; Drouhet, 1955a) and also in the treatment and prevention of infections in humans, especially in patients undergoing treatment with the broad-spectrum antibiotics such as the tetracyclines (Drouhet, 1955b; Sarewitz, 1955; Childs, 1956; Stewart, 1956). The successful treatment of patients with primary infections with candida have been reported by Sloane (1955), Robinson (1955), and Stewart (1956). Recently vaginal pessaries containing nystatin became available, and we report here the treatment with these pessaries of 53 patients suffering from vaginal candida infections, and in order to assess the value of this treatment the results obtained are compared with those in 36 patients treated with gentian violet.

Clinical Investigation

We included in this investigation only those women who were complaining of a vaginal discharge and/or irritation, and who were found to have candida infection bacteriologically. Two positive cultures were obtained from most patients—one on the first attendance at the clinic and one immediately before the first treatment. The women were divided into two comparable groups—one group to be treated with nystatin, and the other with a 1% aqueous solution of gentian violet. All patients were seen by one of us (J. D. Ll.-J.) and all had the typical lesions associated with candida infection. Anyone who had an associated trichomonal vaginitis was excluded.

Initially, treatment was carried out on three alternate days, on each occasion the vagina being inspected with a speculum for lesions before its commencement. Treatment consisted in the insertion of two pessaries containing 100,000 units of nystatin or, in the control group, in painting out the vagina with a 1% aqueous solution of gentian violet.

All patients were asked to attend one week after the completion of the treatment, when the vagina was inspected for lesions and a swab taken for bacteriological examination. In the case of a negative swab being obtained, the patients were asked to attend one month later for a final examination. If candida was still present on either occasion, treatment was continued for a further week, and a swab taken a week after completion, as before. Most of the patients in the gentian-violet series who did not respond after one week were transferred to the nystatin series, together with six women in whom gentian violet caused a severe local reaction necessitating termination of treatment. There were no adverse local reactions to nystatin.

Bacteriological Examination

All the swabs were inoculated on to blood agar and Littman's medium; smears were also examined microscopically. The Littman's plate was incubated for three to five

days before a negative report was given. All the strains of *Candida* isolated were subcultured on to corn-meal agar, so that the identification of *C. albicans* by chlamydospore formation could be made. Four strains not producing chlamydospores were further examined. Their fermentation reactions resembled *C. krusei*, but their morphological appearance was not typical. Sensitivity tests were carried out on all strains by serial dilution in broth and by blotting-paper disks (Jennison and Stenton, to be published). The average minimal inhibiting concentration at 48 hours in the broth was 3.6 µg. per ml. (2,800 units=1,000 µg.). No evidence of the development of resistance appeared in this series.

Results

In Table I the bacteriological findings after treatment with nystatin are compared with those obtained in the control group treated with gentian violet. The number of patients

TABLE I.—Comparison of Bacteriological Findings One Week After Treatment with Gentian Violet and Nystatin

	Gentian Violet			Nystatin		
	No. Treated	Candida		No. Treated	Candida	
		Present	Absent		Present	Absent
Pregnant ..	13	9	4 ($\chi^2=2.8$)	16 ($0.1 > P > 0.05$)	5	11
Non-pregnant	23	10	13 ($\chi^2=7.3$)	19 ($P < 0.01$)	0	19
Total ..	36	19	17 ($\chi^2=10.0$)	35 ($P < 0.01$)	5	30

who were bacteriologically free from infection one week after the cessation of treatment was significantly higher in the nystatin series. Some of the patients from whom candida was grown after treatment were in fact free from symptoms, and no lesions could be seen on clinical examination. Three of the failures with nystatin were in pregnant women who were delivered before a second course could be given; the other two were re-treated, one being cured. Four of the failures with gentian violet were re-treated with gentian violet with no effect.

TABLE II.—Effect of Treatment with Nystatin on Patients not Cured by Gentian Violet

	No. Treated	Candida	
		Present	Absent
Pregnant ..	6	0	6
Non-pregnant ..	12	4	8

TABLE III.—Total Number of Patients Treated with Nystatin, Including Five after Second Course

	No. Treated	Cured	
		No.	%
Pregnant ..	22	18	82
Non-pregnant ..	31	29	93
Total ..	53	47	88

Table II shows the effect of treatment with nystatin on patients who failed to respond to or who had a reaction with gentian violet. All the latter group were cured by one course of nystatin. Three of the four failures were re-treated, with a successful result in two.

The results in all 53 women treated with nystatin are shown in Table III. A notable feature of this treatment has been the large number of patients who stated that their symptoms were relieved after the first day of treatment. The number of patients cured refers only to those who were bacteriologically negative one week after the cessation of treatment and does not include some patients who, although clinically cured, still harbour candida organisms.

All the patients apparently cured after one week were asked to attend four weeks later for reassessment. Some of

the patients had been delivered, but 11 out of a possible 16 of the gentian-violet series and 34 out of 47 of the nystatin series did attend, and the relapse rates are shown in Table IV. Three of the women who had been treated with nystatin were seen by colleagues at about the appropriate time and were free from obvious infection.

TABLE IV.—Relapse Rate in Patients Seen Four Weeks After Cessation of Treatment

	Gentian Violet			Nystatin		
	No. of Patients	Candida Present	Relapse Rate	No. of Patients	Candida Present	Relapse Rate
Pregnant ..	2	2	100%	14	4	29%
Non-pregnant ..	9	3	33%	20	3	15%
Total ..	11	5	46%	34	7	21%

Discussion

Although the patients treated with nystatin had only a short course of treatment the results have proved to be most promising and distinctly better than those in the patients treated with gentian violet in a comparable scheme. Moreover, treatment with the nystatin pessaries is much simpler and does not have the disadvantage of staining linen, etc., as does gentian violet. The insertion of the pessaries could be easily done by the patient, thus saving much time for the patient and for the nursing and medical staffs. Also, as nystatin acts mainly on fungi and yeasts and has very little effect on bacteria, it means that there is much less interference with the normal flora than is the case with gentian-violet treatment.

Relapses, which are probably reinfections, are less frequent after nystatin than after gentian violet. It has been shown that oral nystatin greatly reduces the yeast population of the intestinal tract (Sternberg *et al.*, 1953), and it may be that combined oral and local treatment may clear the more persistent or recurrent infections. Sarewitz (1955) reported five cases of genito-urinary infection with candida which were improved or cured by oral therapy. We have treated one patient with oral tablets alone (500,000 units thrice daily for one week) with an excellent result, there being no symptoms and the culture being negative after six weeks. However, as there is no good evidence that high blood levels can be obtained by oral therapy it is unlikely that better results would accrue from this method alone. In fact, Childs (1956) has noted that systemic treatment had little or no effect on the numbers of candida organisms in the sputum and throat. Stewart (1956) and Childs (1956) reported nausea as a side-effect of oral nystatin, and our patients also complained of nausea with some abdominal pain.

Summary

Of 53 women with monilial vaginitis treated with a new vaginal pessary containing 100,000 units of nystatin, 47 (88%) were free from infection one week after treatment, whereas of 36 treated with gentian violet, only 17 (47%) were cured.

Out of a group of 18 who had not responded to gentian violet, 16 were cleared with nystatin.

In the patients seen four weeks after treatment the relapse rate was 46% in those treated with gentian violet and 21% in those treated with nystatin.

No side-effects or local discomfort has occurred with nystatin, whereas six of the women treated with gentian violet had a reaction which made it necessary to stop treatment.

One patient was treated with oral nystatin only, with an apparent cure.

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THE BREATH IN ACUTE LEUKAEMIA

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It is well known that a fetid breath may be found in patients with leukaemia in association with lesions of the upper alimentary and/or respiratory tracts. These lesions may be gum hypertrophy, petechiae and ecchymoses, or oozing of blood, gingivitis and mucosal ulceration, and necrosis. The smell is presumed to arise from the bleeding and from secondary infection.

Over the last few years some patients have been seen in whom acute leukaemia was accompanied by a peculiar sweet odour of the breath resembling that of a freshly opened corpse, but not associated with clinical involvement of the gums, mouth, or upper respiratory or alimentary tract. As the smell of the breath was of assistance to me in the clinical diagnosis of some of these patients, the results are recorded of my findings from this aspect in 73 cases of leukaemia which presented in hospital practice. In each case the presence or absence of halitosis was confirmed by at least one other medically qualified observer.

The 73 cases comprised 51 cases of acute leukaemia (34 myeloblastic, 15 monoblastic, 2 erythro-leukaemic) and 22 cases of the chronic group (11 granulocytic, 11 lymphocytic).

Results

Of 51 cases of acute leukaemia, 12 (9 myeloblastic, 3 monoblastic) had the characteristic halitosis without obvious clinical involvement of the mouth or respiratory and alimentary tracts (see Table). In six of these (Cases 5-10)

Blood Picture in the 12 Cases of Acute Leukaemia with Characteristic Halitosis

Case No.	Sex	Age in Years	Type of Leukaemia	Hb (%)	Total W.B.C./c.mm.	Blast Cells/c.mm.
1	M	17½	Myeloblastic	82	3,000	1,230
2	F	49	"	70	4,000	1,040
3	M	71	"	58	1,000	520
4	M	2½	"	35	4,000	2,000
5	M	18	"	40	200,000	198,000
6	M	29	"	88	5,000	600
7	M	41	"	47	23,000	12,420
8	M	9	"	35	13,000	9,880
9	F	46	"	45	5,000	550
10	M	28	Monoblastic	48	24,000	2,880
11	M	68	"	63	45,000	14,950
12	F	44	"	47	80,000	12,000

there were other signs and symptoms such as splenomegaly, etc., which suggested the true diagnosis. Clinical examination of the remaining six patients (Cases 1-4, 11, and 12) helped very little, for they had no sternal tenderness, haemorrhagic lesions, hepato-splenomegaly, or lymphadenopathy, and it was only after examination of the blood and bone marrow that a firm diagnosis could be made. One patient (Case 1) had had an appendectomy followed by