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Humoral immunity to *Malassezia furfur* serovars A, B and C in patients with pityriasis versicolor, seborrheic dermatitis and controls

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Abstract: This study examined the humoral immune responses to *Malassezia furfur* serovars A, B and C of 10 patients with pityriasis versicolor, 10 patients with seborrheic dermatitis and 20 age- and sex-matched controls. A transferable solid-phase ELISA was used to determine titres of total Igs, IgM, IgA and IgG specific to *M. furfur* serovars A, B and C. The results demonstrated that patients with seborrheic dermatitis had a significantly higher titre of total Igs to serovar A than patients with pityriasis versicolor; and that patients with seborrheic dermatitis had a significantly higher titre of IgA to serovar C than patients with pityriasis versicolor. The titres of total Igs for controls and patients with seborrheic dermatitis were significantly lower to serovar B than to serovar C. A modified TSP ELISA was used to determine the titres of the IgG subclasses. Titres of $IgG_{1,3,4}$ to serovar B were significantly higher in seborrheic dermatitis patients than pityriasis versicolor patients and titres of IgG_3 to serovar A were significantly higher in seborrheic dermatitis patients than pityriasis versicolor patients. However, despite the differences between the patient groups, none of these results was significantly different to those of controls. Thus, this study did not demonstrate any differences in humoral immunity of patients suffering from *Malassezia*-associated dermatoses when compared to normal controls. These results may suggest that the humoral immune response to *M. furfur* is not related to the pathogenesis of *Malassezia*-associated dermatoses, but simply to the carriage of *M. furfur* on the skin.

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Key words: *Malassezia furfur* – pityriasis versicolor – seborrheic dermatitis – enzyme-linked immunosorbent assay – IgG subclasses

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Introduction

Many investigators have determined the antibody titres specific to *Malassezia furfur* in patients with *Malassezia*-associated dermatoses in attempts to elucidate the part that the humoral immune response plays in the pathogenesis of the diseases. However, as with much of the work on *Malassezia*, the results generated have been conflicting. In general, the literature can be divided into two: studies which found elevated antibody titres to *M. furfur* in patients (1, 2, 3) and studies which found no difference in antibody titres to *M. furfur* in patients when compared to controls (4, 5). Several groups of workers used quantitative immunofluorescent titration (1, 2, 4, 5, 6) whilst another used an enzyme linked immunosorbent assay (3) (ELISA). Different groups also used different antigenic preparations in the assays, including whole cells, disrupted cells and cytoplasmic preparations. All these variables make it impossible to compare the results obtained by different groups and largely explains the disparity in the literature.

DaMert et al. (1) and Wu & Chen (2) measured the antibody titres specific to *Malassezia* in patients with pityriasis versicolor using immunoflu-

orescence with whole cell antigens. Both studies found that the antibody titres in patients were significantly higher than those of controls. However, Furukawa et al. (4) and Faergemann (5) also used immunofluorescence and whole cell antigens to determine antibody titres specific to *Malassezia*, but did not find any differences between patients with pityriasis versicolor and controls.

Bergbrant et al. (6) estimated the IgG titres specific to *Malassezia* in 30 patients with seborrheic dermatitis using immunofluorescence and whole cell antigens and compared them to 57 healthy individuals and found no significant difference. Midgley & Hay (3) also measured the antibodies to *Malassezia* in 40 patients with seborrheic dermatitis and 40 age- and sex-matched controls. They used an ELISA method with cytoplasmic extracts as antigens and found that patients had a higher mean titre than controls.

Cunningham et al. (7) studied the antibodies in 60 normal individuals of various ages to *M. furfur* serovars A, B and C. They developed a transferable solid phase (TSP) ELISA and found that individuals had demonstrable antibody titres to *M. furfur* by the age of 2–3 years. The titres of IgG and IgM did not differ between the children and the adults. The only difference in titres in relation to the age of the subjects was a lower IgM titre in the 60–64 year old group compared to the younger groups. Titres of IgA were found to be low or undetectable.

Although many studies have examined the titres of total Igs, IgM and total IgG specific to *Malassezia*, the titres of the four IgG subclasses have never been determined. Measurement of total IgG may mask an imbalance of the IgG subclasses, which may be relevant in the pathogenesis of the diseases. Cunningham et al. (7) used the three serovars of *M. furfur* as antigens when measuring antibody titres in normal volunteers, but this is the first time that the serovars have been used as antigens for determining antibody titres in patients with dermatoses.

The aim of this study was to measure the antibody titres specific to *M. furfur* serovars A, B and C in patients with pityriasis versicolor and seborrheic dermatitis and controls, using a TSP ELISA. Titres, specific to *M. furfur* serovars A, B and C, of total Igs, IgM, IgA, total IgG and the subclasses of IgG (IgG_{1-4}) were determined for the patients and controls.

Material and methods

Reagents

An AlaSTAT total IgE kit was obtained from Diagnostic Products Corporation, USA. Bovine serum albumin (BSA), Tween 20 and phosphatase substrate were obtained from Sigma, UK. Sodium carbonate, sodium bicarbonate, magnesium chloride hexahydrate and diethanolamine were obtained from British Drug Houses, UK. The ELISA was carried out in plasticware obtained from Nunc Ltd (Gibco). Affinity purified, alkaline phosphatase conjugated goat anti-human Igs, IgM, IgA, IgG and rabbit anti-sheep IgG were obtained from Sera Lab. The antisera used for the determination of IgG subclasses were affinity-purified sheep anti-human IgG_{1-4} from The Binding Site, UK.

Patient and control subjects

Two groups of patients were studied, both of which were attending the dermatology outpatient clinics at Leeds General Infirmary. Neither group of patients was receiving antimicrobial therapy at the time of the study or for 2 weeks previously. The first group consisted of 10 patients with pityriasis versicolor, which was defined as scaly hypo or hyperpigmented lesions with minimal erythema. Lesional sites were the chest (10/10) and the back (8/10) and all patients had moderate disease. The patients with pityriasis versicolor had a mean age of 34.0 yr (age range 23–41 yr). The second group consisted of 10 patients with seborrheic dermatitis, which was defined as scaly, moderately inflamed itchy lesions. Lesional sites were the forehead (5/10), chest (3/10), back (2/10), left and right cheeks (3/10), chin (1/10) and temples (1/10). None of the patients had scalp lesions and all had moderate disease. They had a mean age of 34.9 yr (age range 25–46 yr). The control group consisted of 20 age- and sex-matched volunteers with no previous history of either pityriasis versicolor or seborrheic dermatitis who were not taking antimicrobial therapy at the time of sampling. Their mean age was 34.1 yr and the age range 23–45 yr.

Determination of total immunoglobulin and complement protein levels

Total IgM, IgA, IgG, C3 and C4 levels were measured in the sera of subjects using a Behring Nephelometer Analyser, with an endpoint method after 6 min incubation. The assay procedure was designed such that at the maximum soluble concentration of the protein in serum, antigen excess did not occur. Total IgE levels were determined, according to the manufacturer's instructions, using an AlaSTAT total IgE kit. The kit used a tube ELISA method

and the inclusion of calibrators allowed a standard curve to be plotted and the concentration of IgE to be calculated in IU/ml.

Determination of total immunoglobulin, IgM, IgA and IgG titres specific to M. furfur *serovars A, B and C*

Cunningham et al. (7) developed a method for measuring the titres of IgM, IgA and IgG specific to *M. furfur* serovars A, B and C. The method consisted of a transferable solid phase (TSP) coated with mid-exponential phase *M. furfur* cells as the antigen in an ELISA. The antigen-coated plates were blocked in wash buffer [0.05% (v/v) Tween 20 and 1% (w/v) BSA] for 16 h at 4°C, air dried and stored at 4°C for up to 2 wk. Before use the TSP's were pre-wet for 5 min in wash buffer. Dilutions of the patient and control sera were made in round-bottomed microtitre (MT) plates and the TSP's immersed in them for 2 h at room temperature (RT). The TSP's were then washed twice for 5 min in wash buffer and incubated in further round-bottomed plates containing the optimal dilutions of anti-human Igs (1 : 500), IgM (1 : 750), IgA (1 : 300) or IgG (1 : 750) for 3 h at RT. After two further washes, the TSP's were placed in flat-bottomed MT plates containing alkaline phosphatase substrate. The substrate (p-nitrophenyl phosphate) was prepared in diethanolamine buffer [diethanolamine 9.7% (v/v), $MgCl_2 \cdot 6H_2O$ 0.01% (w/v), NaN_3 0.02% (w/v); pH 9.8] at a concentration of 1 g/l, immediately before use. The reaction was allowed to proceed until the positive control serum on each plate had reached a pre-determined optical density (OD) value, at which point the reaction was stopped by the addition of 3 M NaOH. The absorbance of each well was then read at 405 nm using a Dynatech MR 7000 ELISA plate reader. The positive control serum had previously been assayed against each antibody for each serovar and the OD values noted after the substrate reaction had proceeded for 30 min. Inclusion of this positive control serum on every assay plate allowed the extent of the reaction to be standardized. A dilution series of negative control serum was also included on each assay plate. The negative control serum was pooled AB serum which had been sequentially absorbed with formalized mid-exponential phase *M. furfur* serovars A, B and C. The titres of IgM, IgA and IgG were calculated as the last dilution of serum with an OD (405 nm) which was double the negative control at the same dilution and above a cut-off value of 0.02 OD units. For Igs the titre was the last dilution of serum with an OD which was double the negative control serum at the same dilution, but with a cut-off value of 0.1 OD units. The titre was expressed as the mean reciprocal $\log_2$ titre.

Determination of IgG subclass titres specific to M. furfur *serovars A, B and C*

The TSP ELISA was modified to measure the titres of IgG subclasses specific to *M. furfur* serovars A, B and C. The TSP's were pre-wet for 5 min in wash buffer and incubated in dilutions of the patient and control sera for 1.5 h at RT. The TSP's were then washed twice and incubated in the optimal dilutions of the relevant sheep anti-human IgG subclass antisera (1 : 50) for 1.5 h at RT. After 2×5 min washes, the TSP's were immersed in rabbit anti-sheep alkaline phosphatase conjugate (1 : 600) for 2 h at RT and finally washed twice. The TSP's were then incubated in alkaline phosphatase substrate until the positive control serum reached a pre-determined OD value, then the reaction was stopped by the addition of 3M Na OH. The OD value of each well was determined using a Dynatech MR 7000 ELISA plate reader. The titres of the IgG subclasses were calculated as the last dilution which had a mean OD value 0.05 OD units greater than the negative control serum at the same dilution.

Statistical analyses

The data for the total immunoglobulins and complement protein levels were analyzed by analysis of variance (ANOVA) (8), and the results expressed as mean level ±95% confidence limits. Antibody titres specific to *M. furfur* were normalized by conversion to the reciprocal $\log_2$ titre, analyzed using analysis of variance and the results expressed as the mean reciprocal $\log_2$ titre ±95% confidence limits. The minimum significant difference (MSD) was calculated from the ANOVA using the T'-method and means which differed by greater than the MSD were significantly different at $p<0.05$.

Results

Determination of total immunoglobulin and complement protein levels

The levels of total IgM, IgA, IgG, C3 and C4 were determined for both groups of patients and age- and sex-matched controls. The results were compared using 1-way ANOVA and no significant differences were found in either the total immunoglobulin levels or the levels of total C3 or C4 in patients with pityriasis versicolor or seborrheic dermatitis when compared to normal controls ($p>0.05$).

The total IgE levels, as measured by the AlaS-

TAT total IgE kit, for patient with either pityriasis versicolor or seborrheic dermatitis and controls, ranged from 0–25.4 IU/ml. The mean±95% confidence limits for the patients with pityriasis versicolor was 3.30±2.62 IU/ml and for the controls 1.44±2.08 IU/ml. For patients with seborrheic dermatitis the mean was 3.70±5.87 IU/ml and for controls 1.55±2.73 IU/ml. All results fell within the normal range as stated for the assay. Thus, there was no difference in the titres of total IgE between patients with pityriasis versicolor or seborrheic dermatitis and controls.

Determination of total immunoglobulin, IgM, IgA and total IgG titres specific to M. furfur *serovars A, B and C*

The mean reciprocal $\log_2$ titre ±95% confidence limits for the total immunoglobulins, IgM, IgA and total IgG specific to *M. furfur* serovars A, B and C are shown in Table 1.

The mean reciprocal $\log_2$ titre of total immunoglobulins ranged from 6.2 (pityriasis versicolor patients to serovar A) to 9.7 (seborrheic dermatitis patients to serovar C). The titre to serovar A was significantly lower in patients with pityriasis versicolor than patients with seborrheic dermatitis ($p<0.05$). Analysis of the data also revealed that both the control group and patients with seborrheic dermatitis had a significantly lower mean reciprocal $\log_2$ titre to serovar B than to serovar C ($p<0.05$).

The mean reciprocal $\log_2$ titre of IgA to *M. furfur* serovars A, B and C ranged from 3.2 (patients with pityriasis versicolor to serovar C) to 6.7 (patients with seborrheic dermatitis to serovar C). When analyzed, this difference was significant with a significantly lower response to serovar C by patients with pityriasis versicolor when compared to the response of patients with seborrheic dermatitis to serovar C ($p<0.05$).

The mean reciprocal $\log_2$ titres of IgM and IgG to *M. furfur* serovars A, B and C were not significantly different either between the serovars or between the groups. Titres of IgM varied from 3.0 (patients with seborrheic dermatitis to serovar B) to 5.0 (patients with seborrheic dermatitis to serovar C), whilst titres of IgG varied from 4.6 (patients with pityriasis versicolor to serovar A) to 7.8 (patients with seborrheic dermatitis to serovar A).

Determination of IgG subclass titres specific to M. furfur *serovars A, B and C*

The mean reciprocal $\log_2$ titre ±95% confidence limits of IgG_{1-4} specific to *M. furfur* serovars A, B and C for patients with pityriasis versicolor, with seborrheic dermatitis and controls are shown in Figs. 1–4 respectively.

As can be seen in Fig. 1, the magnitude of the IgG_1 response of patients with pityriasis versicolor to serovar B was significantly lower than that of patients with seborrheic dermatitis to serovar B ($p<0.05$). The titres ranged from 3.3 (pityriasis versicolor patients to serovar B) to 6.2 (seborrheic dermatitis patients to serovars B and C).

The mean reciprocal $\log_2$ titre of IgG_2 specific to the three serovars of *M. furfur* ranged from 4.4 (patients with pityriasis versicolor to serovars B and C) to 6.2 (controls to serovar B). However,

Table 1. Mean reciprocal $\log_2$ titre ±95% confidence limits of total immunoglobulins, IgA, IgM and IgG specific to *M. furfur* serovars A, B and C

		Malassezia furfur serovar		
		A	B	C
Igs	PV	6.2±2.2] p<0.05	7.7±1.3	7.6±1.6
	SD	9.4±1.6]	7.0±1.7	9.7±1.2
			└ p<0.05 ┘	
	Con	7.8±1.5	6.8±1.0	8.9±0.9
			└ p<0.05 ┘	
IgA	PV	6.1±2.1	5.0±2.0	3.2±1.3] p<0.05
	SD	5.4±2.0	5.7±2.6	6.7±1.7]
	Con	5.5±1.0	5.9±1.5	3.9±1.0
IgM	PV	4.4±0.9	3.7±0.8	4.6±1.5
	SD	4.1±1.0	3.0±0	5.0±1.6
	Con	4.2±1.0	3.4±0.6	4.6±0.8
IgG	PV	4.6±2.0	6.8±2.0	5.3±2.6
	SD	7.8±2.6	7.0±2.8	7.7±2.8
	Con	6.2±1.6	7.6±1.7	7.0±1.9

PV=Pityriasis versicolor patients. SD=Seborrheic dermatitis patients. Con=Controls.

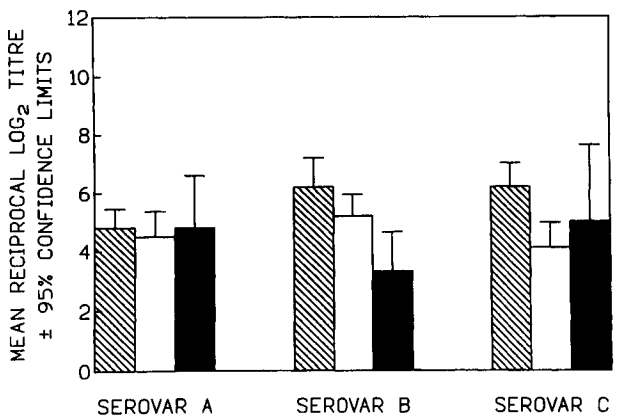

Figure 1. The mean reicprocal $\log_2$ titre of IgG_1 specific to *M. furfur* serovars A, B and C for patients with seborrheic dermatitis; pityriasis versicolor and controls. ▨ Seborrheic dermatitis patients. □ Age- and sex-matched controls. ■ Pityriasis versicolor patients. Results are expressed as the mean reciprocal $\log_2$ titre ±95% confidence limits.

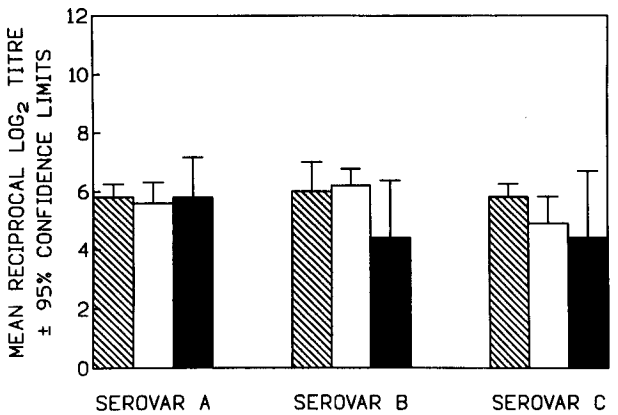

Figure 2. The mean reciprocal $\log_2$ titre of IgG_2 specific to *M. furfur* serovars A, B and C for patients with seborrheic dermatitis, pityriasis versicolor and controls. ▨ Seborrheic dermatitis patients. □ Age- and sex-matched controls. ■ Pityriasis versicolor patients. Results are expressed as the mean reciprocal $\log_2$ titre ±95% confidence limits.

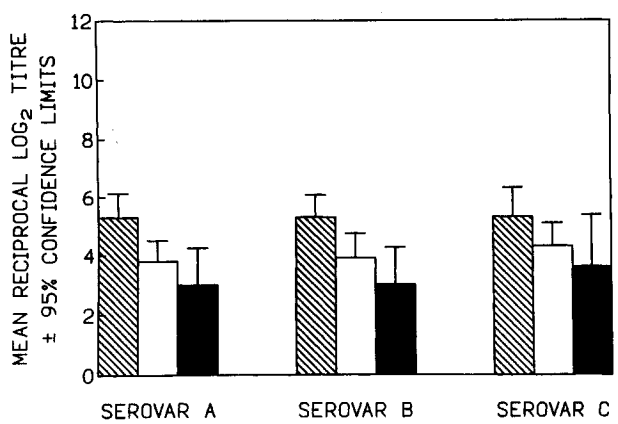

Figure 3. The mean reciprocal $\log_2$ titre of IgG_3 specific to *M. furfur* serovars A, B and C for patients with seborrheic dermatitis, pityriasis versicolor and controls. ▨ Seborrheic dermatitis patients. □ Age-and sex-matched controls. ■ Pityriasis versicolor patients. Results are expressed as the mean reciprocal $\log_2$ titre ±95% confidence limits.

there were no significant differences in the titres between the groups or the serovars.

For IgG_3, the mean reciprocal $\log_2$ titre ranged from 3.0 (patients with pityriasis versicolor to serovars A and B) to 5.3 (seborrheic dermatitis to serovars A, B and C). The titres of patients with pityriasis versicolor were significantly lower to both serovars A and B than those of patients with seborrheic dermatitis ($p<0.05$).

The mean reciprocal $\log_2$ titre of IgG_4 ranged from 3.7 (patients with pityriasis versicolor to serovar A) to 6.2 (patients with seborrheic dermatitis to serovar B). The titre of patients with pityriasis versicolor was significantly lower to serovar B than that of patients with seborrheic dermatitis ($p<0.05$).

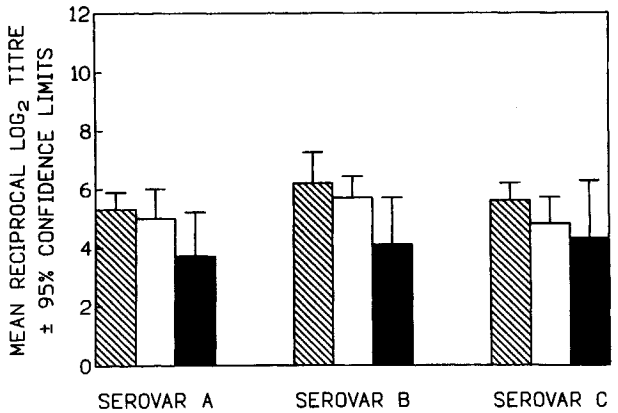

Figure 4. The mean reciprocal $\log_2$ titre of IgG_4 specific to *M. furfur* serovars A, B and C for patients with seborrheic dermatitis, pityriasis versicolor and controls. ▨ Seborrheic dermatitis patients. □ Age- and sex-matched controls. ■ Pityriasis versicolor patients. Results are expressed as the mean reciprocal $\log_2$ titre ±95% confidence limits.

Discussion

The aim of this study was to determine whether patients with pityriasis versicolor or with seborrheic dermatitis exhibited different patterns of antibody titres to *M. furfur* serovars A, B and C when compared to each other and to age- and sex-matched controls. In addition to studying the antibodies specific to *M. furfur*, the total levels of IgM, IgA, IgG, IgE, C3 and C4 were measured to ensure that none of the patients or controls was immunocompromised. Statistical analysis revealed that there were no differences in the levels of total IgM, IgA, IgG, C3 or C4 between any of the groups, illustrating that these patients did not appear to have any general humoral immune deficiency which predisposed them to the dermatoses. This differs from the findings of Wu & Chen (2) who stated that in 30 patients with pityriasis versicolor the titres of total IgG and IgM were significantly higher than those of 30 age- and sex-matched controls. However, they did not state what statistical method had been used. Bergbrant et al. (6) found that for 30 patients with seborrheic dermatitis, 14 and 11 had "higher than normal" total IgG and total IgA respectively. Because no statistical analysis was presented, it is not known whether this was sufficient to cause a significant difference between the two groups.

Many workers have studied the pattern and magnitude ofthe humoral response to *M. furfur* in patients with either pityriasis versicolor or seborrheic dermatitis, using a variety of methods. However, Bergbrant et al. (9) compared several methods for their ability to detect antibodies specific to *M. furfur* and they found that the ELISA

was the only method sensitive enough to detect differences in antibody titres. Cunningham et al. (7) developed a transferable solid phase ELISA to measure antibodies specific to *M.furfur* serovars A, B and C and this was used in this study to determine antibody titres in patients with pityriasis versicolor or seborrheic dermatitis and controls.

Several conclusions were drawn from the results of this present study. Firstly, the pattern and magnitude of titres of IgM and IgG did not differ significantly between either the patients and controls or the serovars. The level of the response of both classes of these two immunoglobulins was not altered in the presence of disease. This suggests that in normal individuals as well as patients with *Malassezia*-associated dermatoses, *M. furfur* is presented to the immune system constantly and initiates both an IgM (naive) and IgG (anamnestic) antibody response. It is possible to speculate on the route by which such sensitization occurs. *Malassezia* has been shown to be a powerful stimulator of the immune response (10) and it may be that cuts, abrasions and any breach of the skin integrity allows sufficient numbers of *Malassezia* to enter the tissues to initiate antibody production. As virtually every person harbors appreciable numbers of *Malassezia* as part of their commensal flora, they will be constantly exposed to its antigens. Midgley & Hay found, using an ELISA method, that the levels of IgG specific to *Malassezia* were higher in patients with seborrheic dermatitis when compared to controls. The problem which arises when attempting to compare the results of different groups is that not only are different methods and antigen preparations used in the assays, but the classifications used for *Malassezia* also vary between groups. The results presented in this study were obtained using an ELISA and whole cells of the three serovars of *M. furfur* as antigens. The serovars of *M. furfur* have not been used previously as antigens for the determination of antibody titres in the sera of patients, and thus, may partly explain the differences observed between this work and that of previous studies.

The second finding of this study was that, although there were several individual differences in the immunoglobulin titres between groups, a consistent pattern which emerged was that where significant differences did occur, patients with seborrheic dermatitis had higher titres than did patients with pityriasis versicolor. This suggests that in general patients with seborrheic dermatitis have a greater degree of exposure to the antigens of *M. furfur*, resulting in higher antibody titres than patients with pityriasis versicolor. There are two pieces of clinical evidence which might provide an explanation for this finding. Firstly, the lesions of seborrheic dermatitis are more markedly inflammatory than those of pityriasis versicolor, suggesting that more leukocytes are present in the lesions of seborrheic dermatitis, allowing for a larger degree of interaction between *M. furfur* and the immune system. Secondly, itching and therefore scratching and abrasion are associated with seborrheic dermatitis which also would present more opportunity for the interaction of *M. furfur* with the immune system.

This study is the first to measure the levels of IgG subclasses specific to *M. furfur*. The measurement of total IgG to *M. furfur* serovars A, B and C did not show up any differences in responses between the groups; however, measurement of IgG subclasses demonstrated significant differences. Patients with seborrheic dermatitis had significantly higher titres of $IgG_{1,3,4}$ to serovar B and IgG_3 to serovar A, than did patients with pityriasis versicolor. This may simply reflect the greater sensitization of patients with seborrheic dermatitis which was seen for the total immunoglobulin and IgA titres. However, two other important conclusions can be drawn from the IgG subclass results. The first is that the titres of all four subclasses were within broadly the same range, which contrasts with the proportions of $IgG_{1\ 4}$ in normal human serum which are 65, 25, 6 and 4% respectively (11). The second relates to the differing properties of the IgG subclasses. The subclasses possess different properties *in vivo* and *in vitro*, such as ability to activate complement and susceptibility to enzymic digestion and cryoprecipitation respectively (12). The subclass produced differs with the antigen, with protein antigens tending to elicit IgG_1 and IgG_3 antibodies whilst carbohydrate antigens tend to elicit IgG_2antibodies. Thus, the presence of $IgG_{1,2,3}$ antibodies to all the serovars of *M. furfur* in all three groups suggests that both the protein and carbohydrate antigens of *M. furfur* are recognized by the immune system and elicit an immune response. It has been suggested that IgG_4 is a late antibody response to high levels of antigens and thus represents a marker of chronic antigen exposure (12). Hence, the relative enrichment of IgG_4 seen here in patients and controls indicates chronic antigen exposure to the serovars of *M. furfur*.

Despite the differences seen between the two patient groups, none of these results was significantly different to those of controls. Thus, this study did not demonstrate any differences in humoral immunity of patients suffering from *Malassezia*-associated dermatoses when compared to normal controls. These results, in conjunction with those of Cunningham et al. (7), may suggest that humoral immunity to *M. furfur* is related simply to

its presence on the skin and is a consequence of the dermatoses rather than related to the pathogenesis of pityriasis versicolor and seborrheic dermatitis.

The role of the humoral immune response to skin commensals is poorly understood. The presence of IgG, IgM, IgE and secretory IgA in human sweat has been documented (13, 14, 15) and would present a readily available route for immunoglobulins to gain access to the organisms on the skin. Metze et al. (16) demonstrated, using histochemical techniques, that commensal organisms present on the skin surface of normal subjects were coated with immunoglobulins. They stated that the entire circumference of the *Malassezia* present in the samples were coated by immunoglobulins, as were the fragments of disrupted cells. However, none of the hyphal elements present had any immunoglobulins on their surface. Thus, in people with no dermatological conditions, antibodies directed against commensals are able to reach their target antigens and attach to them. The antibodies might bind to virulence factors which the organism produced or affect their ability to adhere to skin cells. It has not been tested experimentally, but it is possible that the binding of antibodies to the organism might also affect its growth rate. Therefore, the ability of antibodies to bind to skin commensals may be responsible for maintaining the *status quo* in most individuals, and it is only when the balance is disturbed that dermatoses arise.

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