

Dissociative symptoms in female patients with mood and anxiety disorders: a psychopathological and temperamental investigation

G. BERSANI¹, M.A MOSCARIELLO¹, F.S. BERSANI^{1,2}, C. COLLETTI³,
A. ANASTASIA³, E. PRINZIVALLI³, G. VALERIANI^{1,2}, M. SALVIATI²

¹Department of Medical-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Rome, Italy

²Department of Neurology and Psychiatry, Sapienza University of Rome, Rome, Italy

³Department of Neuroscience and Behaviour, Section of Psychiatry, Federico II University of Naples, Naples, Italy

Abstract. – OBJECTIVE: Dissociative symptoms are frequent among psychiatric patients and may considerably affect patients' psychopathological condition and treatment outcomes. The objectives of the study are to assess the presence of dissociative symptoms in female patients with mood and anxiety disorders, to investigate their correlation with the clinical severity of the disorders and to investigate those personality traits that are more frequent in patients with high levels of dissociation.

PATIENTS AND METHODS: 50 Caucasian females were enrolled in the study. Patients were assessed through the Self-Report Symptom Checklist, the Dissociative Experiences Scale (DES) and rating scales for Depression and Anxiety.

RESULTS: The mean DES score in the overall sample was 16.6. 32% of patients had a DES score > 20. Depressive symptoms positively correlated with the DES total scores. Dissociator patients presented some significantly different temperamental characteristics in comparison with non dissociator patients.

CONCLUSIONS: Dissociative symptoms are highly present in patients with mood and anxiety disorders and correlate with the severity of depressive symptoms. Specific personality traits more frequently observed in dissociator people may represent predisposing factors; their early identification could be clinically relevant.

Key Words:

Anxiety disorders, Dissociation, Dissociative symptoms, Mood disorders, Personality traits, Temperament.

DSM-5 dissociative disorders include a range of symptoms and manifestations like derealization, depersonalization, psychogenic amnesia and confusion about one's own identity^{2,3}. For several years, dissociative symptoms (DS) have been considered as border conditions between normality and psychopathology⁴.

It has been shown that DS are phenomena commonly found in the general population^{5,6}. Moreover, DS like depersonalization or derealization are frequent in several psychiatric disorders including panic disorder, obsessive compulsive disorder, post-traumatic stress, insomnia, borderline personality, delirium, conversion disorder, depression and bipolar disorder⁷⁻¹⁹.

DS are often not clinically recognized; this fact may be related to the absence of appropriate diagnostic instruments. Clinicians are often not trained to observe dissociative phenomena and patients have difficulty in spontaneously reporting this kind of experiences⁵.

DS are frequent, with a female male ratio of 9:1, and they may considerably affect patients' psychopathological condition and treatment outcomes^{6,20}. The aims of the present study are (1) to assess the presence of DS in female patients with mood and anxiety disorders, (2) to investigate a possible correlation between the clinical severity of the disorders and DS and (3) to investigate those personality traits more frequent in people with high levels of DS.

Introduction

According to Bernstein and Putnam¹, "dissociation is the lack of normal integration of thoughts, feelings, and experiences into the stream of consciousness and memory". In Both DSM-IV and

Patients and Methods

Sample

Female patients consecutively admitted to the Psychiatric Outpatient Unit of A. Fiorini Universi-

ty Hospital of Terracina, Sapienza University of Rome, were considered for participation in the study. Inclusion criteria were: age 18-75; DSM-IV TR diagnosis of a mood or anxiety disorder; Hamilton Depression Rating Scale (HAM-D) and Hamilton Anxiety Scale (HAM-A) total score ≥ 18 . Exclusion criteria were: illiteracy; psycho-organic deficits; co-morbidity with psychotic disorders.

50 Caucasian females were enrolled in the study; mean age was 46.22 ± 5.51 . 26 patients met criteria for a Mood Disorder (18 Major Depressive Disorder and 8 Bipolar Disorder) and 24 met criteria for an Anxiety Disorder (15 Generalized Anxiety Disorder; 9 Panic Disorder).

The diagnosis was made through the Structured Clinical Interview for DSM-IV-TR. Patients were clinically assessed through the following scales: Dissociative Experiences Scale (DES)¹; Temperament and Character Inventory (TCI)²¹; HAM-D²² and HAM-A²³; Self-Report Symptom Check-List (SCL-90)²⁴.

The mean time of administration of scales was 67 min; at the time of clinical assessment 35 patients were drug-free and 21 were under pharmacological treatments.

Clinical Measures

TCI²¹ is an inventory for personality traits. It operates with seven dimensions of personality traits: four temperaments (Harm Avoidance -

HA; Reward Dependence - RD; Novelty Seeking - NS; Persistence - P) and three characters (Self-directiveness - SD; Cooperativeness - C; Self-transcendence - ST).

SCL-90²⁴ is a relatively brief self-report validated questionnaire designed to evaluate a broad range of psychological problems and symptoms of psychopathology. The scale investigates different symptomatological areas such as somatization (SOM), obsession and rituals (OBS), difficulty in relationships (SENS), depressive (DEP) or anxious (ANX) symptoms, violent behaviors or anger (HOST), panic disorder (PHOB), diffidence or paranoia (PARAN) and presence of psychosis (delusions, hallucinations, etc) (PSYC). The Global Severity Index (GSI), that describes the psychopathological distress, was also considered.

DES¹ is a self-rating scale measuring the tendency to experience dissociative states in daily life (total range: 0-100). It includes 3 subscales: Amnesia (AMN), Absorption (ABS) and Depersonalization-Derealization (DEP-DER).

HAM-D²² and HAM-A²³ are validated multiple item questionnaires used to provide an indication of depression and anxiety.

Statistical Analysis

Based on the DES total score, patients with higher presence of dissociative experiences (DES

Table I. SCL-90, TCI and DES scores in the overall sample.

	SCL-90									
	GSI	SOM	OBS	SENS	DEPR	ANX	HOST	PHOB	PARAN	PSYC
Min	0	0	0	0	0	0	0	0	0	0
Max	3.22	3.36	4	3.11	3.75	3.07	3.5	2.71	3.6	3
Mean	1.30	1.33	1.55	0.84	1.46	1.40	0.83	0.57	1.20	0.60
St. Dev	0.73	0.81	1.03	0.89	0.93	0.77	0.84	0.74	0.96	0.71
	TCI									
	NS	HA	RD	P	SD	C	ST			
Min	17.5	37.143	18.75	25	18.182	35.714	18.182			
Max	82.8597	97.143	84.667	100	88.636	92.857	83.704			
Mean	52.29	65.51	55.93	59.25	56.34	71.48	47.89			
St. Dev	14.39	13.24	13.87	21.79	14.47	13.35	16.96			
	DES									
	Total score	AMN	ABS	DEP-DER						
Min	0	0	0	0						
Max	49.75	80	80	77.5						
Mean	16.60	13.12	23.25	13.83						
St. Dev	14.64	17.07	18.01	16.97						

> 20) were separated by those with lower presence, thus dividing the sample in subgroups of “dissociator” (DS+) and “no dissociator” (DS-) patients.

The normal distribution of data was assessed using the Shapiro-Wilk Test. Student’s *t* test was performed to compare psychopathological characteristics of DS+ and DS- subgroups.

The correlation between DES total score and HAM-A, HAM-D, TCI and SCL-90 was calculated using the Pearson’s correlation test.

p < 0.05 was considered statistically significant.

Results

Overall Sample

The mean DES score in the overall sample was 16.6. An higher score was observed in ABS subscale (mean = 23.25) (Table I).

16 patients (32%) had DES scores > 20 and were thus considered “dissociators”; among these, 9 had mood disorders and 6 had anxiety disorders. 36 patients (64%) had DES scores < 20 and were, thus, considered “no dissociators”; among these, 19 had mood disorders and 17 had anxiety disorders.

SCL-90 scores showed a high GSI score (1.30 ± 0.73) (Table I); the subscales with the highest mean scores were OBS (1.55 ± 1.03), DEPR (1.46 ± 0.93) and ANX (1.40 ± 0.77) followed by SOM (1.33 ± 0.81) and PARAN (1.20 ± 0.96) (Table I).

TCI showed high scores in the subscale C (71.48 ± 13.35) and HA (65.51 ± 13.24) (Table I).

Correlation Between DES Total Score and HAM-D, HAM-A, TCI and SCL-90

Pearson’s correlation test gave a weak, positive, linear, significant correlation (*r*: 0.354; *p*: 0.017) between the severity of depressive symptoms (HAM-D scores) and the presence of DS; no significant correlations were found between DES and HAM-A scores. A weak, positive, linear, significant correlation was also found between DES total score and the SD subscale of TCI (*r*: 0.327; *p*: 0.022). No significant correlations were found between DES total score and SCL-90 subscales. More details are given in Table II.

Dissociators (DS+) vs No Dissociators (DS-)

The results of SCL-90 (Table III) indicated that DS+ patients with Anxiety Disorders presented significant differences compared with DS-

patients with anxiety disorders, showing significant higher values in HOST (1.73 vs 0.98, *p* = 0.02) and PARAN (1.90 vs 1.10, *p* = 0.04). Among patients with mood disorder, DS+ patients had higher scores than DS- patients in the GSI (1.71 vs 1.17, *p* = 0.04) and HOST subscales (1.69 vs 0.72 *p* = 0.003).

In relation to TCI scores (Table III), DS+ patients affected by a Mood Disorder presented some significant differences in comparison with DS-; lower values were found in RD (3.01 vs

Table II. Correlation between DES total score and HAM-D, HAM-A, TCI and SCL-90

		DES total score
HAM-A	Pearson’s Correlation	0.216
	Sig. (2-tailed)	0.145
HAM-D	Pearson’s Correlation	0.354*
	Sig. (2-tailed)	0.017
TCI		
NS	Pearson’s Correlation	-0.158
	Sig. (2-tailed)	0.279
HA	Pearson’s Correlation	0.058
	Sig. (2-tailed)	0.690
RD	Pearson’s Correlation	0.255
	Sig. (2-tailed)	0.078
P	Pearson’s Correlation	0.006
	Sig. (2-tailed)	0.967
SD	Pearson’s Correlation	0.327*
	Sig. (2-tailed)	0.022
C	Pearson’s Correlation	0.112
	Sig. (2-tailed)	0.468
ST	Pearson’s Correlation	-0.050
	Sig. (2-tailed)	0.734
SCL-90		
GSI	Pearson’s Correlation	-0.082
	Sig. (2-tailed)	0.585
SOM	Pearson’s Correlation	-0.172
	Sig. (2-tailed)	0.241
OBS	Pearson’s Correlation	-0.142
	Sig. (2-tailed)	0.343
SENS	Pearson’s Correlation	-0.080
	Sig. (2-tailed)	0.582
DEPR	Pearson’s Correlation	-0.150
	Sig. (2-tailed)	0.298
ANX	Pearson’s Correlation	-0.148
	Sig. (2-tailed)	0.307
HOST	Pearson’s Correlation	-0.157
	Sig. (2-tailed)	0.277
PHOB	Pearson’s Correlation	-0.193
	Sig. (2-tailed)	0.180
PARAN	Pearson’s Correlation	-0.056
	Sig. (2-tailed)	0.704
PSYC	Pearson’s Correlation	-0.228
	Sig. (2-tailed)	0.124

**p* < 0.05.

4.26; $p = 0.01$), SD (3.72 vs 4.94; $p = 0.03$) and C (3.09 vs 4.79; $p = 0.03$) subscales. Patients with an Anxiety Disorder showed important differences between the DS+ and DS- groups in NS (4.12 vs 5.50 $p = 0.03$) and HA (6.50 vs 5.00 $p = 0.01$).

Discussion

DS are characterized by a disruption of and/or discontinuity in the normal integration of consciousness, memory, identity, emotion, perception, body representation, motor control, and behaviour; they can potentially disrupt every area of psychological functioning³. 35% of the patients enrolled in this study had frequent DS. This high frequency confirms the results of previous researches highlighting that unidentified DS are often present in patients with other psychiatric diseases: Ball et al²⁵ found that 69% of patients with panic disorder experienced depersonalization or derealization during their panic attacks; similarly, Finnish studies^{7,14} reported high prevalence rates of dissociative symptoms in psychiatric outpatients (14%) and inpatients (21%).

Significant positive correlations were found between the presence of DS and the severity of

depressive symptoms (measured through HAM-D). This result confirms the close association between dissociation and the severity of affective disorders already found in previous studies. In this regard, several reports highlighted the close association between depressive symptoms and dissociation^{13,26,27}: Goff et al²⁸ found that patients with elevated dissociation scores had more severe obsessive-compulsive symptoms, were more depressed, and were more likely to have a personality disorder than patients with low dissociation scores; DS in patients with bipolar disorder seem to be correlated with early onset of the disorder and with panic disorder co-morbidity¹².

DS can considerably influence the symptom profile and response to treatment²⁹; higher levels of dissociation might be a predictor of negative treatment outcome in cognitive-behavioral therapy for patients with anxiety disorders and obsessive compulsive disorder³⁰ and may predict poor outcomes in inpatients participating in brief psychodynamic psychotherapies³¹.

Higher level of dissociation may also directly and indirectly influence the pharmacological treatment. It is known, in fact, that dissociative experiences reduce the response to drug therapy and that there is a negative correlation between DES total score and average dosages of pre-

Table III. Dissociators vs No Dissociators.

	SCL-90 in patients with anxiety disorder			SCL-90 in patients with mood disorder		
	DES < 20	DES > 20	<i>p</i>	DES < 20	DES > 20	<i>p</i>
GSI	1.32	1.44	ns	1.17	1.71	0.04
SOM	2.40	1.86	ns	2.77	1.46	ns
OBS	1.60	1.75	ns	1.98	1.65	ns
SENS	1.33	0.82	ns	1.50	1.12	ns
DEPR	1.52	1.78	ns	1.77	1.55	ns
ANX	1.46	1.78	ns	1.15	1.58	ns
HOST	0.98	1.73	0.02	0.72	1.69	0.003
PHOB	0.93	0.60	ns	0.57	0.68	ns
PARAN	1.10	1.90	0.04	1.66	1.36	ns
PSYC	0.79	1.12	ns	0.90	0.90	ns
	TCI in patients with anxiety disorder			TCI in patients with mood disorder		
	DES < 20	DES > 20	<i>p</i>	DES < 20	DES > 20	<i>p</i>
NS	5.50	4.12	0.03	4.36	4.45	ns
HA	5.00	6.50	0.01	5.97	5.36	ns
RD	3.80	5.00	ns	4.26	3.01	0.01
P	4.11	5.50	ns	4.31	4.63	ns
SD	4.83	5.50	ns	4.94	3.72	0.03
C	4.11	4.50	ns	4.79	3.09	0.03
ST	3.50	4.25	ns	3.57	4.27	ns

scribed medications. Similarly, the prescription of benzodiazepines should be discouraged in people with dissociations, while the use of mood stabilizers, in addition to antidepressants, seems to be a more appropriate strategy^{30,32-36}.

Even if DS influence the symptom profile and the response to treatment, they are often not clinically recognized because of the absence of appropriate diagnostic instruments and because clinicians are often not trained to observe dissociative phenomena, usually being more focused on more evident psychopathological issues. A more adequate and early individuation of DS may strongly aid physicians in achieving better clinical outcomes.

The results of the study also indicate that some specific characterial and temperamental aspects may be related with DS. Personality and temperamental traits like low novelty seeking and high harm avoidance in anxious patients, and like low reward dependence, low self-directedness and low cooperativeness in depressed patients, are more frequent among patients with higher dissociative experiences. As personality typically remains constant throughout life, these personality traits may represent predisposing factors to the development of DS; even if it is not possible to define a category of patients at greater risk of developing dissociative symptoms, the early identification of potentially predisposing personality traits could be clinically helpful. In addition, the presence of personality traits potentially predisposing to the development of DS contributes to raise some doubts on the recurrent idea that DS are exclusively caused by traumatic experiences^{37,38}.

Conflict of Interest

All Authors of this paper have no relevant affiliations or financial involvement with any organization or entity with a financial interest in, or financial conflict with the subject matter or materials discussed in the manuscript.

References

- 1) BERNSTEIN EM, PUTNAM FW. Development, reliability, and validity of a dissociation scale. *J Nerv Ment Dis* 1986; 174: 727-735.
- 2) AMERICAN PSYCHIATRIC ASSOCIATION. *Diagnostic and Statistical Manual of Mental Disorders 4th. Text revision*. Washington, DC: American Psychiatric Association, 2000.
- 3) AMERICAN PSYCHIATRIC ASSOCIATION. *Diagnostic and statistical manual of mental disorders 5th ed*. Arlington, VA: American Psychiatric Publishing, 2013.
- 4) MERCKELBACH H, MURIS P. The causal link between self-reported trauma and dissociation: a critical review. *Behav Res Ther* 200; 39: 245-254.
- 5) KIHLSSTROM JF. Dissociative disorders. *Annu Rev Clin Psychol* 2005; 1: 227-253.
- 6) HUNTER EC, SIERRA M, DAVID AS. The epidemiology of depersonalisation and derealisation. A systematic review. *Soc Psychiatry Psychiatr Epidemiol* 2004; 39: 9-18.
- 7) MAARANEN P, TANSKANEN A, HINTIKKA J, HONKALAMPI K, HAATAINEN K, KOIVUMAA-HONKANEN H, VIINAMÖKI H. Factors associated with pathological dissociation in the general population. *Aust N Z J Psychiatry* 2005; 39: 387-394.
- 8) MOSCARIELLO MM, RATTI F, QUARTINI A, FORCÉN FE, MUNUERA JN, BERSANI G. Dissociative symptoms in patients with mood and anxiety disorders. *Riv Psichiatr* 2010; 45: 234-243.
- 9) MURRAY J, EHLERS A, MAYOU RA. Dissociation and post-traumatic stress disorder: two prospective studies of road traffic accident survivors. *Br J Psychiatry* 2002; 180: 363-368.
- 10) MULDER RT, BEAUTRAIS AL, JOYCE PR, FERGUSSON DM. Relationship between dissociation, childhood sexual abuse, childhood physical abuse, and mental illness in a general population sample. *Am J Psychiatry* 1998; 155: 806-811.
- 11) JOHNSON DM, PIKE JL, CHARD KM. Factors predicting PTSD, depression and dissociative severity in female treatment-seeking childhood sexual-abuse survivors. *Child Abuse Negl* 2001; 25: 179-198.
- 12) MULA M, PINI S, PREVE M, MASINI M, GIOVANNINI I, CASSANO GB. Clinical correlates of depersonalization symptoms in patients with bipolar disorder. *J Affect Disord* 2009; 115: 252-256.
- 13) OEDEGAARD KJ, NECKELMANN D, BENAZZI F, SYRSTAD VE, AKISKAL HS, FASMER OB. Dissociative experiences differentiate bipolar-II from unipolar depressed patients: The mediating role of cyclothymia and the Type A behaviour speed and impatience subscale. *J Affect Disord* 2008; 108: 207-216.
- 14) MAARANEN P, TANSKANEN A, HINTIKKA J, HONKALAMPI K, HAATAINEN K, KOIVUMAA-HONKANEN H, VIINAMÖKI H. The course of dissociation in the general population: a 3-year follow-up study. *Comprehensive Psychiatry* 2008; 49: 269-274.
- 15) ZANARINI MC, RUSER T, FRANKENBURG FR, HENNEN J. The dissociative experiences of borderline patients. *Compr Psychiatry* 2000; 41: 223-227.
- 16) LATALOVA K, PRASKO J, PASTUCHA P, GRAMBAL A, KAMARADOVA D, DIVEKY T, JELENOVA D, MAINEROVA B, VRBOVA K. Bipolar affective disorder and dissociation-comparison with healthy controls. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub* 2011; 155: 181-186.

- 17) MACRÌ F, MINICHINO A, CAMPI S, MARINO M, PANNESE R, DE MICHELE F, CAPRA E, TRABUCCHI G, BERSANI FS. Chronic conversion somatic disorder: a case report. *Recenti Prog Med* 2013; 104: 70-72.
- 18) MINICHINO A, BERSANI FS, CALÒ WK, SPAGNOLI F, FRANCESCONI M, VICINANZA R, DELLE CHIAIE R, BIONDI M. Smoking behaviour and mental health disorders-mutual influences and implications for therapy. *Int J Environ Res Public Health* 2013; 10: 4790-4811.
- 19) BERSANI FS, IANNITELLI A, PACITTI F, BERSANI G. Sleep and biorhythm disturbances in schizophrenia, mood and anxiety disorders: a review. *Riv Psichiatr* 2012; 47: 365-375.
- 20) SPITZER C, KLAUER T, GRABE HJ, LUCHT M, STIEGLITZ RD, SCHNEIDER W, FREYBERGER HJ. Gender differences in dissociation. A dimensional approach. *Psychopathology* 2003; 36: 65-70.
- 21) CLONINGER CR, SVRAKIC DM, PRZYBECK TR. A psychobiological model of temperament and character. *Arch Gen Psychiatry* 1993; 50: 975-990.
- 22) HAMILTON M. A rating scale for depression. *J Neurol Neurosurg Psychiatr* 1960; 23: 56-62.
- 23) HAMILTON M. The assessment of anxiety states by rating. *Brit J Med* 1959; 32: 50-55.
- 24) DEROGATIS LR, SAVITZ KL. The SCL-90-R and the Brief Symptom Inventory (BSI) in Primary Care In: Maruish ME editor. *Handbook of psychological assessment in primary care settings*. NJ: Lawrence Erlbaum Associates, 2000, Volume 236, pp. 297-334.
- 25) BALL S, ROBINSON A, SHEKHAR A, WALSH K. Dissociative symptoms in panic disorder. *J Nerv Ment Dis* 1997; 185: 755-760.
- 26) LIPSANEN T, SAARIJARVI S, LAUERMA H. Exploring the relations between depression, somatization, dissociation and alexithymia-overlapping or independent constructs? *Psychopathology* 2004; 37: 200-206.
- 27) GREENES D, FAVA M, CIOFFI J, HERZOG DB. The relationship of depression to dissociation in patients with bulimia nervosa. *J Psychiatr Res* 1993; 27: 133-137.
- 28) GOFF DC, OLIN JA, JENIKE MA, BAER L, BUTTOLPH ML. Dissociative symptoms in patients with obsessive-compulsive disorder. *J Nerv Ment Dis* 1992; 180: 332-337.
- 29) BRAND BL, CLASSEN CC, McNARY SW, ZAVERI P. A review of dissociative disorders treatment studies. *J Nerv Ment Dis* 2009; 197: 646-654.
- 30) PRASKO J, RASZKA M, ADAMCOVA K, GRAMBAL A, KOPRIVOVA J, KUDRNOVSKÁ H, LATALOVA K, VYSKOCILOVÁ J. Predicting the therapeutic response to cognitive behavioral therapy in patients with pharmacoresistant obsessive-compulsive disorder. *Neuro Endocrinol Lett* 2009; 30: 615-623.
- 31) SPITZER C, BARNOW S, FREYBERGER HJ, GRABE HJ. Dissociation predicts symptom-related treatment outcome in short-term inpatient psychotherapy. *Aus N Z J Psychiatry* 2007; 41: 682-687.
- 32) BRAND BL, LANIUS R, VERMETTEN E, LOEWENSTEIN RJ, SPIEGEL D. Where are we going? An update on assessment, treatment, and neurobiological research in dissociative disorders as we move toward the DSM-5. *J Trauma Dissociation* 2012; 13: 9-31.
- 33) SIERRA M. Depersonalisation disorder: Pharmacological approaches. *Expert Rev Neurother* 2008; 8: 19-26.
- 34) BERSANI FS, CAPRA E, MINICHINO A, PANNESE R, GIRARDI N, MARINI I, DELLE CHIAIE R, BIONDI M. Factors affecting interindividual differences in clozapine response: a review and case report. *Hum Psychopharmacol* 2011; 26: 177-187.
- 35) BERSANI G, MECO G, DENARO A, LIBERATI D, COLLETTI C, NICOLAI R, BERSANI FS, KOVERECH A. l-Acetylcarnitine in dysthymic disorder in elderly patients: A double-blind, multicenter, controlled randomized study vs. fluoxetine. *Eur Neuropsychopharmacol* 2013; 23: 1219-1225.
- 36) BERSANI G, RAPISARDA V, CIANI N, BERTOLINO A, SORGE G. A double-blind comparative study of sertraline and amitriptyline in outpatients with major depressive episodes. *Hum Psychopharmacol Clin Exp* 1994, 9: 63-68.
- 37) KAGAN J. Human morality and temperament. *Nebr Symp Motiv* 2005; 51: 1-32.
- 38) MERCKELBACH H, MURIS P. The causal link between self-reported trauma and dissociation: a critical review. *Behav Res Ther* 2001; 39: 245-254.