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The Measurement of Change in Endogenous Affective Disorders

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Summary. Psychopathological syndromes, as originally revealed by clinical observation, can also be detected by multivariate statistical analyses of symptom ratings. Changes in the course of psychiatric syndromes may be rated simply by improvement scales or by consecutive quantifications of symptoms and their comparison in chronological order. For the latter approach, which is less liable to bias, clinical ratings of psychopathology by staff members, self-ratings by the patients, analyses of patients' overt behavior (including video and speech records), or objective measurements of psychological and/or physiological variables can be used. Advantages and limitations of these different methods are discussed and illustrated by examples from ongoing clinical research in affective disorders. Generally, the combined use of different rating procedures is recommended. Self-ratings are economical, but they may represent aspects of psychopathology other than clinical ratings. In endogenous depression, mood scales are valid (supplementary) tools for the quantification of long-term as well as short-term changes, including diurnal variations. In severe conditions of mania, however, clinical rating has been—until now—the only valid basis for quantifying the degree of psychopathology and its changes with time. Precise evaluation of changes in psychopathology is essential in longitudinal investigations of endogenous affective disorders, since psychopathology up to now seems to have been the most sensitive and the most specific indicator of the hypothetical underlying abnormalities of cerebral functioning.

Key words: Depression – Mania – Syndromes – Measurement of change – Diurnal variations.

Zusammenfassung. Psychopathologische Syndrome, wie sie ursprünglich aufgrund klinischer Beobachtung entdeckt wurden, lassen sich auch durch multivariate statistische Analysen von Symptom-Skalen auffinden. Zeitverläufe

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von psychiatrischen Syndromen können durch einfache Skalierung der Befundänderungen selbst oder (zur Vermeidung von Erinnerungsfehlern) durch den Vergleich wiederholter quantitativer Symptomerfassung objektiviert werden. Für letzteren Ansatz kommen klinisch-psychopathologische Fremdbeurteilungs-Skalen, Selbstbeurteilungs-Skalen, Analysen des beobachtbaren Patientenverhaltens (auch mit Video- und Sprachaufnahmen) oder objektive Messungen psychologischer und/oder physiologischer Variablen in Betracht. Vorzüge und Grenzen der verschiedenen Methoden werden diskutiert und anhand von Beispielen aus laufenden klinischen Untersuchungen über affektive Psychosen erläutert. Grundsätzlich wird die kombinierte Anwendung verschiedener Untersuchungsverfahren empfohlen. Selbstbeurteilungs-Skalen sind ökonomisch, bilden aber teilweise andere Aspekte der jeweiligen Psychopathologie ab als klinische Schätz-Skalen. Bei endogener Depression stellen Stimmungsskalen valide (zusätzliche) Instrumente für die Quantifizierung langfristiger wie kurzfristiger Veränderungen, einschließlich der Tagesschwankungen, dar. Bei schweren manischen Zuständen dagegen bildet vorläufig die klinische Beurteilung die einzige valide Grundlage für die Quantifizierung der psychopathologischen Normabweichungen und ihrer zeitlichen Veränderungen. Die möglichst genaue Messung psychopathologischer Zustandsänderungen ist bei Längsschnitt-Untersuchungen endogener affektiver Psychosen von entscheidender Bedeutung, zumal die Psychopathologie den bis heute sensibelsten und spezifischsten Indikator für die hypothetischen zugrundeliegenden Hirnfunktionsstörungen darzustellen scheint.

Schlüsselwörter: Depression – Manie – Syndrome – Skalierung von Veränderungen – Zirkadiane Periodik.

1. Introduction

By 'endogenous affective disorders,' we designate an interrelated group of psychopathological syndromes (v. Zerssen, 1973) that occur in predisposed individuals and for which neither somatic factors nor psychogenetic mechanisms can provide a sufficient explanation (Mayer-Gross et al., 1969; Schulte and Tölle, 1977). These syndromes were originally revealed by clinical observation and described as mania, depression, or mixed states of both. However, they can also be detected by means of multivariate statistical analyses[1] of comprehensive symptom ratings in heterogeneous groups of psychiatric inpatients (Lorr et al., 1963; Mombour et al., 1973). The kernel syndromes of mania and depression, respectively, are represented by primary factors (Table 1), which together with correlated factors constitute more complex syndromes that correspond with the typical symptom patterns of patients clinically diagnosed as suffering from either mania or depression. This is demonstrated in Figure 1, which shows the respective syndrome score (derived from the IMPS; cf. Lorr and Klett, 1967) of a small group of manic patients.

A typical feature of endogenous affective disorders is their episodic course. The term 'episodic' signifies a return to the premorbid state. Usually this return occurs within a couple of weeks or months (Angst, 1966). Another typical feature is the recurrence of episodes and, though less frequent, the alternation from one

[1] cf. Overall and Klett, 1972

Table 1. Two dimensions (principal components) of psychopathology on the basis of data[a] from inpatients with various kinds of psychiatric disorders ($n = 454$)[b]

Depressive syndrome	Manic-euphoric syndrome
Helpless	Flight of ideas
Disturbances of vital feelings	Elation/euphoria
Discouraged/sad	Increased self-confidence
Hopeless/desperate	Increased energy
Anxious	Motoric unrest
Internally restless	Logorrhea
Feelings of insufficiency	Social overactivity
Guilt feelings	
Amelioration in the evening	
Feeling ill	
Suicidal tendencies	
Difficulties falling asleep	
Difficulties staying asleep	
Shortening of sleeping time	
Tiredness	
Reduced appetite	
Constipation	

[a] Items of the AMP documentation system, part 3: mental symptoms, and 4: somatic signs and symptoms (cf. Scharfetter, 1972)
[b] Mombour et al. (1973)

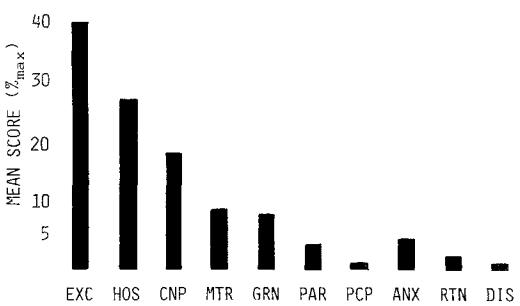

Fig. 1. Mean IMPS scores (for explanation see Table 3) in manic inpatients ($n = 6$)

abnormal state to the other (mania to depression or vice versa), with or without a symptom-free interval. Concomitant fluctuations in mood and behavior are usually observed during an episode. In mania they are rather unpredictable and often obviously related to environmental stimuli. In depression they seem to be less dependent on the environmental situation and, on the whole, more predictable, with worsening in the morning and a reduction in severity in the afternoon or early evening. These changes, however, do not occur in all patients and, in an individual case, not during all his episodes of depression and not even during the whole course of a specific episode (Waldmann, 1972).

There is as yet no solution to the question of how these changes in severity of depression are related to diurnal variations in other aspects of behavior and in

autonomic functions as well as biochemical processes. These relationships can only be analyzed successfully if the variations in question—including those in depression—can be evaluated quantitatively.

Another problem calling for a quantification of changes in the psychopathology of affective disorders arises in connection with the therapy of patients with severe acute mania. Here the spontaneous fluctuations in psychopathology can make it extremely difficult to evaluate the short-term effects of therapeutic measures. This difficulty can only be overcome by adequate measurement of changes in psychopathology in relation to these interventions.

In the present paper, we illustrate some of our approaches to the quantitative analysis of changes in psychopathology during either a depressive or a manic phase. The examples are taken from ongoing research related to diurnal variations in mental, motoric, autonomic, and biochemical processes during a depressive episode (unpublished) and to the short-term influence of β-sympathicolytic treatment on the psychopathology of mania (Emrich et al., in preparation; Rackensperger et al., 1976; v. Zerssen, 1976e).

2. Methodological Considerations

Let us first consider which properties an instrument must possess to be estimated as an adequate measure of change in psychopathology.

There are basically two approaches in this area: the rating of the change itself, usually on the basis of a kind of improvement scale; and the consecutive evaluation of the patients' actual symptomatology. In the latter case, inferences with respect to changes can only be made by comparing the results of evaluations in chronological order (cf. Harris, 1963).

We have chosen the latter approach because it is less liable to distortions of memory. Moreover, it is theoretically applicable to an indefinite number of time sections, thus enabling the investigator to analyze changes that occur within short intervals over a long period of time. This possibility, however, is a necessary prerequisite for either the recognition of regularities of mood changes during a depressive episode and of relations of these changes to changes in other variables or the recognition of intervention effects on the irregularly fluctuating symptomatology of severe mania.

The techniques for a consecutive quantification of psychopathological phenomena are summarized in Table 2 (cf. v. Zerssen, in press). On the left-hand side, the broadest categories are mentioned. They are specified in the middle column and, on the right-hand side, these more specific categories are exemplified by techniques used in our investigations which will be referred to in this presentation. The most general differentiation is that which exists between ratings by judges (usually clinicians, clinical psychologists, or nurses), self-ratings by the patients themselves, analyses of behavior including linguistic analyses of speech or written productions of a patient, and, finally, objective measurements, either of 'spontaneous' activities (motoric, autonomic) or of reactions within a standardized situation (objective psychometric tests).

Clinical rating still is the most comprehensive means of evaluating psychopathology quantitatively (cf. CIPS, 1977; Mombour, 1972; Pichot and Olivier-

Table 2. Methods for a quantitative evaluation of psychopathology

General approach	Specified examples	Instruments used in our studies on affective disorders	Authors (year)
Rating	Clinical rating		
	Global	Global rating scale of depression	Schwarz and Strian (1972)
	Composite unidimensional	Rating scale for depression	Hamilton (1967)
	multidimensional	IMPS	Lorr and Klett (1967)
	Ward behavior rating	NOSIE	Honigfeld and Klett (1965)
		MS scale	Beigel et al. (1971)
	Self-rating		
	Global	Line test	Zealley and Aitken (1969)
	Composite unidimensional	Bf-S/Bf-S′	v. Zerssen (1976b)
	multidimensional	PD-S/PD-S′	v. Zerssen (1976d)
Behavioral/ linguistic analysis	Analysis of social behavior	Video tape recording of visual contact/ speech in interview sessions	Ellgring (1977)/ Emrich and Eilert (1978)
Objective measurement	Assessment of motor activity	Actometer (arm/leg)	McFarlain and Hersen (1974), modified by Emrich et al. (1977)
	Arithmetic test of efficiency	Pauli test (modified)[a]	

[a] Arbeits- und Konzentrations-Testgerät AKTG, provided by ZAK, Simbach/Inn

Martin, 1974). There are, however, some disadvantages inherent in rating procedures. First of all, any kind of rating is in a way subjective and, therefore, liable to bias. The dependency of results on the raters' skills and biases reduces the comparability of ratings done by different observers. Moreover, clinical ratings can usually be adequately performed by a well-trained staff only. Finally, multidimensional ratings, which are, of course, the most informative, are also the most time-consuming for the investigators. From an economic viewpoint, patients' self-rating (cf. CIPS, 1977; Pichot and Olivier-Martin, 1974) may, therefore, be preferable to clinical rating, at least under certain conditions; in general, however, it can only serve as a supplementary tool to clinical rating (v. Zerssen, 1976a).

The last statement is also true for the techniques listed below ratings and self-ratings on our table, e.g., behavioral and/or linguistic analyses and objective measurements (cf. Ciminero et al., 1977; Hersen and Bellack, 1976; v. Zerssen, in press). The results are doubtlessly more resistant to subjective attitudes of the observer and the patient. However, they may not sufficiently reflect the kind of disturbance that has to be evaluated, either because they are too specific to represent a complex phenomenon (like depression) or because they are more closely related to other phenomena than the pathology in question (e.g., motoric activity may reflect ward routines rather than the patient's spontaneous behavior). This leads to the question of validity of measurement, which is linked to the question of reliability (Cronbach, 1964; Lienert, 1969).

In this context the term 'reliability' refers to the consistency of scale values rather than to their constancy over a period of time, because the latter cannot be high if the condition to be measured is in itself an inconstant characteristic. The correlation of equal parts of a complex test usually serves as a measure of consistency. Another measure of cross-sectional reliability is the intercorrelation of scale values obtained by two parallel versions of the same instrument at a given time. In our longitudinal investigation of diurnal variations in endogenous depression, we used a unidimensional self-rating mood scale composed of 28 items (pairs of adjectives that characterize opposite states of mood). This scale (v. Zerssen, 1976b) had been shown to possess an internal consistency of 0.92. The intercorrelation between the two parallel versions of the test had reached the value of 0.86 in a normative sample from the general population. Similar values had been found in samples of psychiatric inpatients. Only if the parallel versions were applied in an interval of one day during a period of rapid change in psychopathology did the intercorrelations drop to lower values (about 0.70). This, however, is an indication of the validity of the test to evaluate changes in psychopathology.

The term 'validity' designates the degree of concordance between scale values and the character in question—in our examples, the extent of affective abnormality. Obviously, this character can only be measured empirically by another instrument so that criterion-oriented validity is, in a way, circularly defined. Expert rating of the character in question is usually regarded as a proper criterion for the evaluation of the validity of a clinical test. For example, our mood scale was partially validated by correlating the scale values with those of Hamilton's clinical rating scale for depression (Hamilton, 1967; cf. Heimann and Schmocker, 1974; v. Zerssen et al., 1974). Depending on the samples under investigation, the

coefficients varied between 0.55 and 0.86, thus pointing to a remarkable degree of concordance between self-rating of mood and clinical rating of depression (cf. v. Zerssen, 1976b).

However, a test can only be regarded as a valid measure of the varying degrees of depressive features in an individual case, if the scale values obtained during consecutive sessions with the same patient correlate highly with an independent clinical rating of the patient's course of depression. This was demonstrated for the preliminary version of our mood scale by the rank correlations between scale values and an independent global clinical rating of depression, each obtained from 10 to 35 consecutive sessions in 28 patients with endogenous depression. The average intraindividual correlation was as high as 0.92 (v. Zerssen et al., 1974). Therefore, the test can be considered to be a highly valid measure of fluctuations in mood during an episode of endogenous depression (the values for neurotic and schizophrenic patients with depressive features are significantly lower than those for patients with endogenous depression). Moreover, the mood scale is a very simple kind of test that can be applied in short intervals of time (e.g., every few hours) without bothering the patient too much.

Similar results can be obtained by using an even simpler method, the so-called line test, which is a kind of a graphical self-evaluation of mood (cf. Zeally and Aitken, 1969). Here the patient has only to indicate his actual mental state on a line, the endpoints of which represent opposite qualities of mood such as extreme well-being and extreme distress. Since this test gives no information on different aspects of mood (represented by the test items of a typical mood scale), the graphical method should be used only as a supplementary tool for the quantification of mood changes, especially if a more detailed analysis of the quality of changes is intended.

There are, of course, many other tests that are sensitive measures of changes in mood or other features of a depressive disorder, but usually these techniques turn out to be rather liable to the effect of exercise, which may obscure the effect of fluctuations in depression. This diminishes their validity for the measurement of change in psychopathology, if the testing has to be done in short intervals of time, as in our study of diurnal variations in mood.

An example of this is an objective psychometric test consisting of simple arithmetic tasks to be solved within a time span of two minutes. The total amount

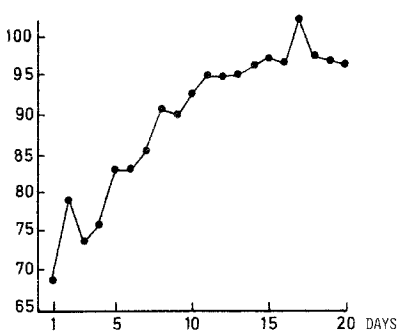

Fig. 2. Daily mean of total score of Pauli test (modified) during a depressive episode in a 33-year-old male inpatient

of solutions can serve as a test score. Figure 2 represents the average values per day of a depressed patient tested daily in intervals of three hours during a drug-free period of 20 days. The score increased gradually during this time, although there was no concomitant amelioration of depressive symptomatology—except on day 8, when the patient seemed somewhat hypomanic (see below). Therefore, the almost constant increase in efficiency during the whole period of testing was apparently due to the effect of exercise and not to a change in psychopathology.

Another mode of objectifying depression, which is less influenced by the repetition of measurements than the majority of objective psychometric tests, is the quantitative analysis of overt pieces of behavior documented by video tapes at consecutive sessions with the same patient. Figure 3 illustrates the results obtained by Ellgring and others at our institute with a depressed patient under therapy with a tricyclic antidepressant (Ellgring, 1977). The lower curve represents (along a reversed scale) the frequency of visual contact with the interviewer during semistandardized interview sessions. Fluctuations in depression are reflected by this simple variable in remarkable concordance with clinical rating (upper curve) and self-rating according to our mood scale, which was filled in by the patient before each session (curve between the two others). The disadvantage of this kind of behavioral analysis is an economic one due to the technical equipment, the trained staff, and the time-consuming scoring procedure required for its implementation. Therefore, it can only be recommended for special programs and not for a more general application in clinical research.

The clinical rating used in the trial just mentioned was based on three subscales of the IMPS (Lorr and Klett, 1967). Each of them represents one primary factor of psychopathology corresponding to a subsyndrome of de-

Table 3. Clinical syndromes according to IMPS factors[a]

Factor	Abbr.	Corresponding clinical syndrome
Excitement	EXC	*Manic-euphoric*
Hostile Belligerence	HOS	*Manic-dysphoric*
Conceptual disorganization	CNP	*Confusional*
Motor disturbances	MTR	*Catatonic*
Grandiose expansiveness	GRN	*Megalomanic*
Paranoid projection	PAR	Paranoid
Perceptual distortions	PCP	Hallucinatory
Anxious depression	ANX	**Depressive**
Retardation and apathy	RTD	**Apathetic**
Impaired functioning	IMP	**State of exhaustion**
Obsessional-phobic	OBS	Phobic-obsessional
Disorientation	DIS	Organic

In italics: Syndromes representing the symptom pattern of mania
Bold face: Syndromes representing the symptom pattern of depression

[a] cf. Lorr (1974); Lorr and Klett (1967); Mombour et al. (1973)

pressive disorders. One of these refers to the kernel syndrome of depression demonstrated in Table 1. The two other syndrome scores entering the total score of depression in this rating, are derived from the factors 'retardation and apathy' and 'impaired functioning' as described by Lorr and co-workers and reproduced in other factor analytic studies with the IMPS (Lorr, 1974), including our own investigations.

In Table 3 the primary factors of the IMPS are related to the corresponding clinical syndromes (cf. Mombour et al., 1973). The intercorrelations of scores representing each syndrome yield a relationship among the three syndromes of depression. Likewise, the five syndromes that are overrepresented in manic psychoses as shown in Figure 1 are positively correlated with one other. In a factorial analysis of syndrome scores of the IMPS (Table 4), one factor (IV) composed of three primary factors of the scale represents depressive disorders, and another one (II) composed of five primary factors represents manic disorders. A third factor (III) comprises a paranoid and a hallucinatory syndrome,

Table 4. Varimax factors of IMPS and KSb-S of psychiatric inpatients ($n = 127$)

		I	II	III	IV	V	VI
KSb-S							
Actual mood	Bf	**0.61**	−0.27	0.16	−0.01	0.32	−0.32
('Befindlichkeit')	Bf'	**0.64**	−0.25	0.02	0.14	0.18	−0.27
Somatic complaints	B	**0.84**	0.05	−0.06	−0.07	0.19	0.16
('Beschwerden')	B'	**0.84**	−0.03	−0.11	−0.06	0.12	0.18
Depression	D	**0.84**	−0.12	0.02	0.03	0.27	−0.01
	D'	**0.85**	−0.01	0.01	0.13	0.14	−0.14
Denial of illness	Kv	**−0.72**	−0.02	0.07	−0.30	0.24	0.03
('Krankheitsverleugnung')	Kv'	**−0.73**	−0.07	0.06	−0.36	0.23	0.06
Paranoid tendencies	P	**0.45**	0.26	**0.41**	**−0.43**	−0.19	0.18
	P'	**0.47**	0.35	**0.48**	−0.23	−0.26	0.19
IMPS							
Excitement	EXC	0.00	**0.83**	−0.11	−0.23	−0.03	−0.16
Hostile Belligerence	HOS	0.06	**0.66**	0.32	0.03	−0.08	−0.14
Conceptual disorganization	CNP	−0.03	**0.80**	0.17	0.00	0.05	0.33
Motor disturbances	MTR	−0.06	**0.66**	0.35	0.29	0.13	0.18
Grandiose expansiveness	GRN	−0.16	**0.72**	0.04	−0.07	−0.07	0.11
Paranoid projection	PAR	−0.19	0.31	**0.81**	0.16	0.05	−0.01
Perceptual distortions	PCP	−0.05	0.05	**0.88**	−0.05	0.05	−0.01
Anxious depression	ANX	0.30	−0.04	−0.08	**0.45**	**0.71**	−0.11
Retardation and apathy	RTD	0.14	−0.07	0.16	**0.71**	0.16	**0.41**
Impaired functioning	IMP	0.39	−0.04	−0.05	**0.62**	0.16	−0.28
Obsessional-phobic	OBS	0.15	0.01	0.07	0.04	**0.81**	0.13
Disorientation	DIS	−0.04	0.10	0.01	0.01	0.06	**0.87**
% Total variance		24.70	14.50	9.90	7.90	7.80	7.10

Bold face: values ≥ 0.40

thus representing a syndrome that can be regarded as the most typical feature of paranoid schizophrenia. A factor combining a phobic-obsessional syndrome and a syndrome of anxious depression (V) mainly reflects neurotic symptomatology, whereas another factor constituted by disorientation and apathy (VI) can be considered as reflecting chronic organic brain disorders.

This factorial structure is rather similar to those found by other investigators on the basis of the subscales of the IMPS (Behrends et al., 1971; Lorr, 1974). Basic methodological differences of our analysis compared with previous studies are the inclusion of a higher percentage of neurotics in the patient sample and the inclusion of self-rating scales in the test variables. Each of these scales was represented by two parallel versions, both related to the same basic aspect of subjective abnormality (cf. v. Zerssen, 1976a). The respective aspects are the actual state of mood at the time of testing (evaluated by our mood scale Bf-S/Bf-S'; v. Zerssen, 1976b), somatic complaints (B-L/B-L'; v. Zerssen, 1976c), and psychic manifestations of anxiety and/or depression (D-S/D-S'; v. Zerssen, 1976d) and paranoid ideation (P-S/P-S'; v. Zerssen, 1976d); in addition, a tendency to a denial of symptoms was evaluated by a control scale (Kv-S/Kv-S'; v. Zerssen, 1976d).

It is remarkable that the common variance of the patients' self-evaluations of abnormality gives rise to one main factor (I; cf. Table 4) that is almost independent of the factors of clinical ratings of psychopathology. There is only a slight correspondence of clinical ratings of depression with the patients' self-ratings.

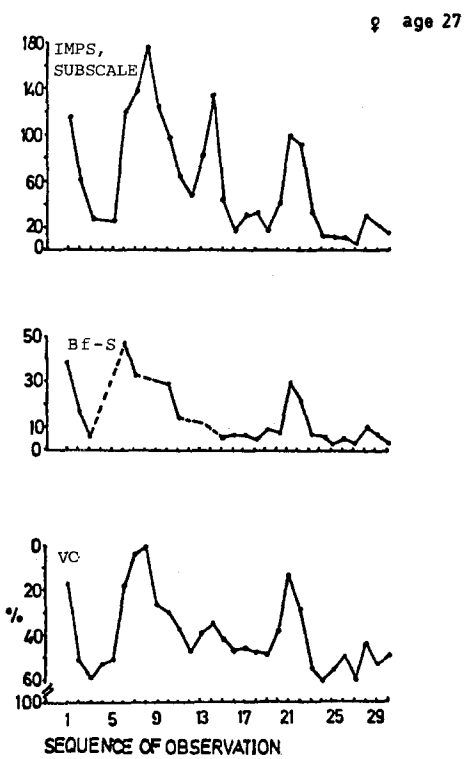

Fig. 3. Course of an endogenous depression (ICD no. 296.2) as reflected by clinical rating (IMPS), self-rating (Bf-S), and systematic observation of visual contact (VC; cf. Ellgring, 1977)

Table 5. Structure of six KSb-S factors of psychiatric inpatients after rotation according to the scree test ($n = 127$)[a]

Variables	I	II	III	IV	V	VI	h^2
Bf	**0.88**	0.21	−0.10	0.04	−0.05	0.03	0.83
Bf′	**0.84**	0.21	−0.22	−0.01	−0.03	0.10	0.81
B	0.31	**0.87**	−0.21	0.13	0.02	−0.04	0.92
B′	0.28	**0.85**	−0.32	0.03	−0.08	−0.03	0.91
D	**0.56**	**0.61**	−0.26	0.22	−0.12	0.00	0.82
D′	**0.69**	**0.46**	−0.28	0.25	−0.08	−0.02	0.84
Kv	−0.19	−0.30	**0.86**	−0.12	0.07	0.01	0.89
Kv′	−0.25	−0.23	**0.86**	−0.14	−0.11	0.06	0.89
P	−0.04	0.26	−0.05	**0.88**	−0.04	0.12	0.86
P′	0.19	−0.05	−0.17	**0.90**	0.02	−0.04	0.88
Information	−0.10	−0.06	−0.03	−0.02	**0.97**	0.18	0.99
Social strata	0.09	−0.04	0.05	0.06	0.18	**0.97**	0.99
% Total variance	21.61	19.64	15.43	14.53	8.53	8.40	88.14

[a] From v. Zerssen (1976a)

There is, however, a definite relationship of the self-evaluation of paranoid ideation with the IMPS superfactor of paranoid and hallucinatory symptomatology (III; cf. Table 4). This finding indicates that self-ratings and clinical ratings may represent different aspects of a patient's mental state (Fahy, 1969). This is particularly true for cross-sectional analyses of psychopathology, but it has also to be considered in longitudinal studies. Thus, the measurement of change in psychopathology cannot be based on self-ratings alone unless a remarkable concordance with clinical ratings or other valid criteria of change has been demonstrated for the subject under investigation. This was demonstrated before for the measurement of change in depressive mood during episodes of endogenous depression (Fig. 3). But there is reason to believe that manic behavior is not adequately reflected by the scores of self-rating scales and should, therefore, be evaluated clinically. The five subscores of the IMPS represented in Figure 1 and Table 3 lend themselves to this evaluation.

Contrary to manics, patients with endogenous depression are usually rather cooperative in clinical investigations and tend to rate changes of their own mental state in relatively high concordance with clinical ratings. This has already been mentioned. We now have to consider whether our mood scale simply reflects a general tendency to complain, as may be concluded from the results of factor analysis of the self-rating scales and the subscales of the IMPS.

Table 5 demonstrates the results of a factor analysis of the same self-ratings in the same sample of psychiatric inpatients as in Table 4 after exclusion of the clinical rating scales (v. Zerssen, 1976a). These were substituted by two other variables, namely, verbal intelligence according to the subtest 'information' of the Wechsler scale (Wechsler, 1958) and a social rating according to professional data. In this analysis the parallel versions of the self-rating scales cluster together in separate

factors. The only exception is found with respect to the scale for the evaluation of psychic manifestations of depression and/or anxiety (D-S/D-S'; v. Zerssen, 1976d). This scale enters two factors that are mainly constituted by other scales, one (I) by our mood scale (Bf-S/Bf-S'; v. Zerssen, 1976b), the other one (II) by the scale representing somatic complaints (B-L/B-L'; v. Zerssen, 1976c). Denial of complaints (Kv-S/Kv-S'; v. Zerssen, 1976d), however, and paranoid ideation (P-S/P-S'; v. Zerssen, 1976d) are clearly separated from each other and from the scales which are mainly related to affective disturbances of an anxious-depressed type, e.g., actual mood and somatic concern. It is also evident from this analysis that self-rating is almost completely independent of verbal intelligence and social strata which are represented in factors V and VI, respectively.

The results of this analysis, which are in accordance with the findings in the normative sample from the general population (cf. v. Zerssen, 1976a), indicate that our mood scale reflects an aspect of subjective abnormality that is broadly related to depression. According to the results of clinical validation studies mentioned earlier, subsequent application of the scale in patients with endogenous depression reveals fluctuations in clinical symptomatology that agree with the results of clinical rating and/or behavioral analysis. For all the reasons mentioned here, it can be regarded as an adequate instrument for the quantification of diurnal variations in endogenous depression.

3. Results of Clinical Investigations

3.1 Psychobiology of Depression

In our longitudinal analyses of the psychobiology of endogenous depression with special reference to diurnal variations[2], a series of measurements is taken in short intervals (every 3 h from 7 a.m. to 10 p.m. and once a night at 2:30) during a drug-free period of 5—22 days (period 1) and, with some exceptions, during the first weeks of subsequent drug treatment (period 2). After full recovery, the measurements are repeated in the same way during a drug-free period of two weeks in all patients (period 3). For the sake of illustration, we select here only a few of the measurements representing the mental, motoric, autonomic, and biochemical spheres, respectively.

In Figure 4, periods 1 and 2 of the first episode of a psychotic depression in a male inpatient aged 33 years are represented by the sequential measurements of mood (diagram 1 according to our mood scale, diagram 2 according to the line test), body temperature (diagram 3), and urine excretion of free cortisol (diagram 4). The two treatment periods are separated by a time span of several weeks during which ECT was applied and drug treatment with amitriptyline and a major tranquilizer was started at another ward. It can easily be recognized that the scores of both the mood scales were highly elevated during the drug-free period 1. Irregular mood changes are apparent in the data, but cannot be clearly evaluated because of the frequency of missing data, particularly during the nights,

[2] This investigation is performed by an interdisciplinary research group at our institute (cf. Schulz et al., this vol. pp. 225—241)

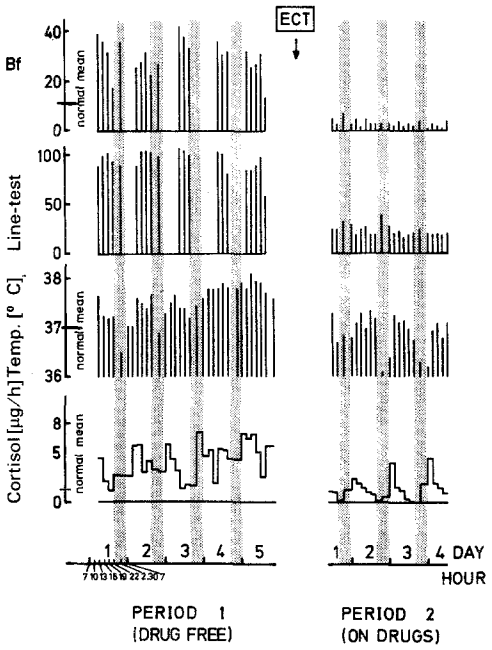

Fig. 4. Diurnal variations in mood and biological variables during a depressive episode in a 33-year-old male inpatient

when the patient was least cooperative. After ECT, under drug treatment the scores of both the mood scales dropped considerably to normal or even subnormal values, indicating a normalization of mood with a slight tendency toward hypomania (period 2).

The lower two diagrams reflect concomitant changes in the other variables: body temperature exhibiting a tendency to abnormally increased values and to an irregularity of diurnal variations before treatment (cf. Pflug et al., 1976) shows a completely normal pattern in period 2, and the excretion of free cortisol (cf. Carroll, 1977) has decreased from an initially highly elevated level to normal values. Unfortunately, during the intensive treatment period with ECT between the two periods plotted in the figure, a complete series of measurements could not be obtained. Therefore, it is not possible to decide whether the amelioration in mood was preceded, accompanied, or followed by the changes in body temperature and cortisol excretion.

In another male patient (also 33 years of age) who was less seriously ill from a depressive episode of a bipolar manic-depressive disorder, the drug-free period could be extended up to three weeks. During this time the patient experienced a sudden, but short-term, hypomanic mood swing after one week of observation. This is reflected by the 'valley' at day 8 in the upper diagram of Figure 5, representing the scores of our mood scale. For the time before and after this hypomanic state, a rather regular diurnal variation in mood was documented by the scale values. At the average, the values are elevated above the normal mean and show a peak in the morning as an expression of the typical features of depressive mood changes during daytime also observed clinically by doctors and nurses. These changes were not so obvious in the data obtained by the line test. We have,

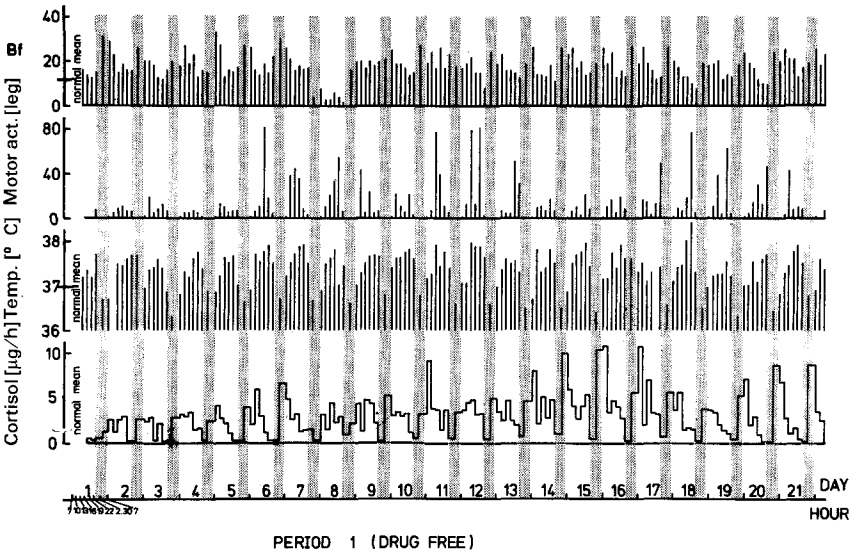

Fig. 5. Diurnal variations in mood and biological variables during a depressive episode in a 33-year-old male inpatient

therefore, replaced this variable by the recording of motor activity of the right leg (see Table 2) as an expression of 'spontaneous' motoric activity (cf. McFarlain and Hersen, 1974). On the basis of these data, we can analyze the question of whether the worsening of mood in the morning and the hypomanic mood swing during day 8 are reflected by changes in the motoric, autonomic, and hormonal spheres, and, if so, which of all the changes precedes the others.

As can be noticed on the diagrams below that representing mood changes, there are no concomitant changes in the other variables. In general, the diurnal variations are regular, following the pattern of healthy individuals (cf. Aschoff, 1976), and there are no obvious deviations from the normal mean values. The fluctuations of variables beyond diurnal variations seem to be irrelevant (as in the case of body temperature) or independent of the hypomanic mood swing at day 8. This is particularly true for the excretion of free cortisol, which is slightly increased on some of the days.

It may be concluded from our examples that there is no simple relation between changes in depressive mood and changes in other variables represented by our measurements. Most likely, all these changes reflect fluctuations in an underlying abnormality of cerebral functioning, but with varying degrees of sensitivity and specificity. Up to now, psychopathology seems to be the most sensitive and most specific indicator of these hypothetical processes. Therefore, it is an important task of longitudinal investigations during depressive episodes to evaluate changes in psychopathology as precisely as possible.

3.2 β-Sympathicolytic Medication in Mania

It was already mentioned that the measurement of change in the psychopathology of mania is usually more difficult than it is in depressive disorders, because

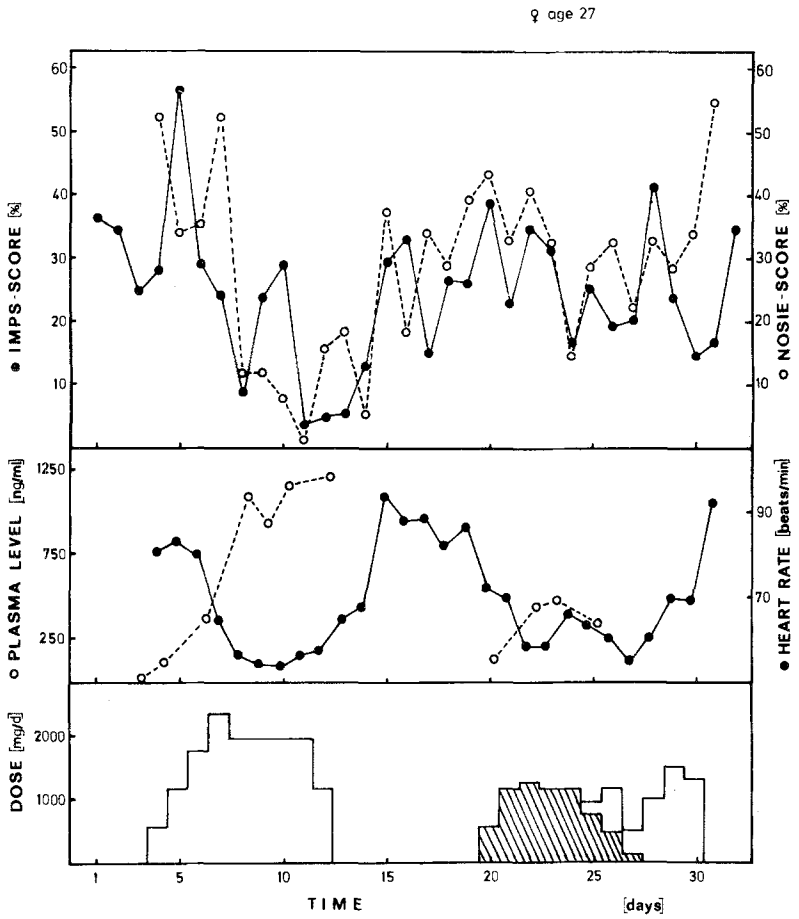

Fig. 6. Course of an endogenous mania (ICD no. 296.1): clinical ratings (IMPS and NOSIE), heart rate, plasma level, and daily oral dose of medication (white histograms = d-propranolol, shaded histogram = dl-propranolol, placebo not indicated)

manics tend to be much less cooperative than depressives so that self-rating and most of the objective psychometric tests cannot be accomplished. In our psychopharmacological investigation on the short-term influence of β-sympathicolytic drugs on the symptomatology of severe mania, it was not even possible to register 'spontaneous' motor activity by simple pedometric recording: some patients were not willing to wear the instrument and some even destroyed it (cf. Rackensperger et al., 1976). Consequently, it was decided to rely exclusively on clinical rating procedures. To maintain a check on their validity, two different approaches were used, one by psychiatric rating according to a comprehensive clinical rating scale (the IMPS) and the other one by nurses' rating according to a ward behavior rating scale for the evaluation of psychotic behavior (the NOSIE; cf. Honigfeld and Klett, 1965). The latter scale was chosen because our nursing staff was accustomed to its usage and hence no special training was necessary. Compared with a unidimensional psychiatric rating scale for mania (e.g., Beigel et al., 1971),

the advantage of the IMPS is that—by the inclusion of syndromes that are unrelated to mania—the symptom pattern of maniform schizoaffective psychoses can also be taken into account. Moreover, in a longitudinal investigation a syndrome shift from mania to depression or other disorders (e.g., a paranoid or an organic symptom pattern) can be evaluated. Compared with the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962), the IMPS is more comprehensive, thus allowing a more detailed analysis of changes in symptomatology.

During the observation period, the patients received either (dl-) propranolol or the stereoisomere (d-propranolol[3]) of its β-sympathicolytic component (l-propranolol) or placebo. The psychiatrist in charge of the IMPS rating was not informed about the actual medication[4].

Figure 6 represents the course of the trial in a manic woman, 27 years of age, whose symptomatology had responded very well to high doses of propranolol during a former episode of her illness. The present trial was carried out in the sequence: placebo—d-propranolol—placebo—propranolol—d-propranolol—placebo, which she finally refused to take because of the high number of pills (30 per day) so that we had to put her on neuroleptic drugs.

The dosage of the medication is represented by the histograms on the bottom line. By the application of placebo, the number and the appearance of pills were kept constant during the whole trial. The plasma level of the pharmacological substances is plotted above the histograms (dotted lines) together with the pulse rate (full line). It can be seen that there is a considerable drop in the pulse rate under propranolol as well as under d-propranolol, and that much higher blood levels of d-propranolol are required to obtain the same effect as with propranolol. This effect is partly due to beta-blockade[5] (which is, of course, much more pronounced with propranolol than with d-propranolol) and partly due to membrane stabilization (which is equal in both stereoisomeres: cf. Barrett, 1975). The mechanisms involved are discussed in another paper (Emrich et al., 1977).

In this context, the upper curves in Figure 6 are of particular interest. They represent the scale values of the NOSIE (dotted line) and the sum total of the scores of five IMPS subscales (full line) belonging to the symptom pattern of mania as pointed out earlier. The general concordance of the independent ratings by a psychiatrist and by nurses is obvious during the whole period of observation. Despite the fluctuation in psychopathology reflected by the ups and downs of the curves, there is a tendency to lower values during active medication with either drug than during the application of placebo, though this tendency is not so marked as it is with respect to the pulse rate.

Judging from this impression, d-propranolol does not only influence the pulse rate (to a minor degree than propranolol), but also possesses antimanic properties. Therefore, the antimanic effect of high doses of propranolol, which was observed

[3] This compound is contaminated with up to 3% l-propranolol (compared with 50% contained in the racemic mixture propranolol)

[4] The rating was performed in the afternoon and took into account observations made during the respective day (and not only during the interview session) so as to diminish variations in psychopathology that were unrelated to the medication

[5] This compound is contaminated with up to 3% l-propranolol (see foot note [3])

in earlier studies, seems to be at least partially due to pharmacological mechanisms other than the blockade of central β-adrenergic receptors. This problem can only be solved on the basis of carefully controlled clinical trials including proper measurements of psychopathology. Such measurements make it possible to analyze the dose-effect relationship of the drugs quantitatively, as will be shown in a publication that is being prepared. In that paper and in a previous one (Rackensperger et al., 1976), a syndrome shift from a purely or predominantly manic symptom pattern to a paranoid one is also dealt with. This shift is of particular interest from clinical and pharmacological viewpoints. In the present paper, however, we have restricted ourselves to the exemplification of the methodological approach to the measurement of change in the psychopathology of affective disorders.

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[6] CIPS = Collegium Internationale Psychiatriae Scalarum

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