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A SPECIFIC LABORATORY TEST FOR THE DIAGNOSIS OF PRIMARY DEPRESSION

A Review Results

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The research in biological psychiatry has recently more and more concentrated on the study of neuroendocrine relationships in psychiatric disorders, mainly on the control of hypothalamic-adrenal *(HPA)* axis in affective disorders (review see in Volšan, Höschl 1977). Concentration on this topic culminated in the studies of B. J. Carrol and his coworkers (Carroll et al., 1976a; Carroll et al., 1976b; Carroll et al., 1981; Carroll, 1982) who presented a comprehensive report of their results of dexamethasone suppression test *(DST)* in depressed patients. Their results, showing that there occurs early escape of plasma cortisol after oral administration of 1 mg dexamethasone given at the time of secretion minimum (11.30 PM) in significant number of patients, stimulated on one hand further efforts in searching for possible variables influencing the *DST* performance, e.g. age (Crumley et al., 1982; Robbins et al., 1982; Poznanski et al., 1982; Spar and Gerner, 1982; Tourigny et al., 1981), current medication (Aimoto et al., 1981; Privitera et al., 1982; Sachar et al., 1980; Brown, Shuey, 1980; Feinberg et al., 1981; Sachar et al., 1981; Butler et al., 1968; Ornstová and Jaššová, 1983), alcohol abuse (Majumdar et al., 1981; Sturtevant and Sturtevant, 1981; Sturtevant et al., 1981; Oxenkrug, 1978), heredity (Rudorfer et al., 1982; Coryell et al., 1982, Schlesser et al., 1980; Winokur et al., 1978), body weight (Gerner and Gwirtsman, 1981; Gwirtsman and Gerner, 1981; Berger et al., 1982), psychogenic pain and pain of organic origin (Blumer et al., 1982; Lascelles et al., 1973), stress (Pancheri et al., 1980) and others (Carroll et al., 1976b) and

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on the other hand the discussion of the causes of DST positivity (Meltzer et al., 1982; Collu, 1977; King, 1975; Carroll et al., 1978) as well as of the present-day diagnostic system structure in psychiatry (Schlesser et al., 1980; Spitzer et al., 1977; Coryell et al., 1982b; Murphy, 1981; Carroll et al., 1981). The discussion is still open. With regard to the importance of this topic and the range of relevant information, which is not sufficiently represented in our literature, we would like to present in more detail various aspects of *DST* and thus give an introduction to, and a discussion of, our work.

1. DIAGNOSTIC ASPECTS OF AFFECTIVE DISORDERS

In spite of the fact that depressive disorders are among the most widespread and serious (suicide) problems in psychiatric medicine, their differential diagnosis is so far rather vague and extensive despite the prima facie greater comprehensibility of depressive symptomatology to physicians (compared e.g. with schizophrenia). In clinical practice, depressions are usually divided into *endogenous (ED)*, mostly supposed to be of biological origin and relatively independent on exogenous psychological influences, and *neurotic* respectively *reactive*, the roots of which are rather sought in interpersonal relations, family atmosphere, life events etc. Clinical picture of both these groups is defined mostly by description of patient's statements, behavior and history, but often also ex post by the psychopharmacological treatment sensitivity. According to various psychiatric textbooks diurnal variations of the state (worse mornings in *ED*), course characteristics (rather periodical in ED with seasonal dependence), or symptom characteristics (e.g. late insomnia rather in ED, early insomnia rather in neurosis) etc. have additional discriminative value. However, other psychopathological criteria may be also added, e.g. aetiopa thogenetic ones, and so classification of depressions is not yet possible according to a single diagnostic axis. We can for example distinguish depressions[1] as

short-term or prolonged reactions comprehensively connected with an appropriate life-event,

neurosis, where the connection with the causal events is not so clear and finding it should be the psychotherapeutic aim,

endogenous (functional) disorder, where central synaptic noradrenergic and/or serotoninergic deficiency and receptor sensitivity changes (Sulser et al., 1978; Vetulani and Sulser, 1975) are supposed to be dominant (e.g. deficient alpha--adrenergic forebrain receptors (Checkley et al., 1982),

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[1]) I.e. states characterized by sadness, hopelessness, self-reproach, self-abhorrence, insufficiency, hypochondria, various somatic complaints, suicidal thoughts or attempts, sleep disorders, sexual dysfunctions, anxiety, worries about minor matters, loss of interest, pessimism, loss of concentration, pains, heavy feelings, anorexia or bulimia, psychomotor retardation or agitation, sometimes even obsessions, derealizations and paranoid symptoms etc.

masked depression, "depressio sine depressione", where the psychopathology is overshadowed by dominant somatic symptoms

symptomatic depression, which is secondary to some somatic illnesses,

depression accompanying organic brain diseases (atrophy, inflammation, tumor, injury, metabolic and toxic disorders)

"pharmacogenic" depression, e.g. in connection with long-term neuroleptic treatment, after reserpine administration in internal medicine (which is often explained on the basis of catecholamine theory of affective disorders as reserpine has indirect symphatheticolytic properties), in the application of hormonal contraceptives (liver tryptophan-pyrrolase induction is supposed to induce the production of kynurenin rather than serotonin, or *MAO* increase is thought to be the cause (Burdwick, 1976) etc.

a part of clinical picture of *other psychiatric disorders*, e.g. alcoholism, drug abuse, anorexia nervosa, personality disorders, sexual disorders, schizoaffective or even schizophrenic disorder etc.

In addition, depressive disorder is often classified as psychotic or nonpsychotic according to its severity. In psychotic affective disorder the catathymic distortion of thought content is expressed to such an extent that thought disorders fulfil the delusion criterion (mostly depressive, delusional selfdepreciation, self-reproach, nihilism, delusions of eternity, hypochondric delusions etc.) and short-term hallucinations fitting in the entire picture can occur as the case may be. If the depressive symptomatology occurs in temporal connection with critical life periods (delivery, climacteric period), one can speak about the so called "generation" disorders (including former diagnosis of "lactation psychosis" — depressive type). Similarly has been defined the involutional melancholia. From these standpoints the connotation of the term "melancholia" is not yet fixed in our sociocultural zone: the term "melancholia" is being used once for deep depression, another time for endogenous depression, psychotic depression, involutional depression, typologically (according to Hippocrates) etc. We deliberately do not extend the topic of this paper to problems of mania, which forms a part of the so called manic-depressive disorder (bipolar depression, cyclophrenia) with various possible temporal characteristics. At present the bipolar depression is often divided in *bipolar I* (with manic phases) and *bipolar II* (with periods of hypomania). Bipolar is understood in contrast to unipolar. The characteristics of unipolar and bipolar depression are presented from the clinical psychopharmacological research standpoint for example by Akiskal and McKinney, 1975.

Such classification has, it is true, some didactic value, but from the logical point of view it is believed to be unsatisfactory, too much like the classification of hats as hard ones, green ones and caps, and at present it is often criticized. In this critical period for psychiatric diagnostics, an effort to unify the diagnostics of affective disorders goes hand in hand with biochemical and psychopharmacological research, for the time being at least in order to facilitate the interpretation of the results

obtained in different parts of the world. The research diagnostic criteria *(RDC)* (Feighner et al., 1972; Spitzer et al., 1977) belong to the most wellknown classification systems of this kind. The criteria define in a similar way as the botanical key the so called Major depressive disorder *(MajDD)* and Minor depressive disorder *(MinDD)*. *MajDD* is further classifiable into primary *(PMajDD)*, which is not preceded in the same patient by other psychiatric disorders, such as panic, phobic or obsessive-compulsatory syndroms, Bricquet's syndrome, antisocial personality, alcoholism, drug dependence, genuine homosexuality, schizophrenia and severe somatic illnesses, which could either dramatically change the life conditions of the patient or which are connected with marked psychopathology (e.g. thyreotoxicosis), and secondary *MajDD*, where the development of depressive symptomathology is preceded by some of those disorders. *RDC* further distinguishes recurrent *MajDD* (in patients having two or more episodes of *MajDD* separated by at least two months lasting remission and being not bipolar), psychotic *MajDD* (when delusions, hallucinations or depressive stupor occur), incapacitating *MajDD* (for patients incapable of any activity or self-care), endogenous *MajDD* (being not dependent on precipitating factors), agitated *MajDD* (accompanied by motor excitation), retarded *MajDD* (slow psychomotor activity, monotony), situational *MajDD* (e.g. depressive reaction fulfilling the criteria for *MajDD*), simple *MajDD* (defined similarly to the primary one, but with a premorbid history of at most one year). The difference between *MajDD* and *MindDD* is defined mainly by the degree of expressed symptomatology, which is for the most part identical with the list stated above.

Psychoneuroendocrinological studies use increasingly the five-axial classification *DSM-III* (Diagnostical and Statistical Manual of Mental Disorders, 3rd edition, Washington, D.C., A.P.A., 1980). *DSM-III* represents atheoretic multiaxial system enabling to classify every case according to certain axis that is always connected with various categories of information: The first axis is related to clinical syndroms and some other conditions, the second axis includes personality disorders and specific developmental disorders and conditions, the third axis includes physical disorders and conditions, the fourth axis includes psychosocial stressors, and the fifth axis includes the highest level of adaptive functioning past year. *DSM-III* is derived from *RDC* and represents an atheoretic concept applicable as a universal network to incoming data, which is open to further discoveries and informations among other things also from the field of biological psychiatry. An example of five-axial classification according to *DSM-III:* Axis *I:* Major depression, single episode, with melancholia (defined in *DSM-III*); alcohol dependence, at present in remission. Axis *II:*: Dependent personality. Axis *III:* Alcoholic liver cirrhosis. Axis *IV:* Psychosocial stressors: expected retirement and change of residence connected with loss of friends (+ quantitative evaluation of severity). Axis *V:* Functional adaptation during the past year: good (quantitatively expressed). *DSM-III* distinguishes the so called major affective disorders including (besides mania) also major depression that is characterized by mood disorder, loss of interests, appetite disorder[1], sleep

disturbance[1], psychomotor disorder[1], fatigue, feelings of uselessness and guilt, poor concentration, indecision, thoughts of death etc. Major depression is divided into following types: Major depression in remission, psychotic depression (delusions and hallucinations), depression with melancholia (qualitatively different feeling of sadness, the depression is worse in the morning, late insomnia, marked psychomotor retardation or agitation, significant anorexia or weight loss, excessive or inappropriate guilt) or without melancholia respectively, and unspecified depression. Bipolar dosorder — presently manic, depressive or mixed respectively — is also distinguished. Major depression may occur in a single episode or be recurrent (if not bipolar). *DSM-III* further classifies "other specific affective disorders" including cyclothymic disorder and dysthymic disorder (depressive neurosis). Atypical affective disorders include atypical bipolar disorder *(bipolar II* in *RDC)* and atypical depression (for patients otherwise nonclassifiable because of various reasons). *DSM-III* has, regardless of its unconventionality, a lot of advantages, among others as a suitable base of knowledge for psychiatric expert consultation systems making the diagnosis on the principle of artificial intelligence, such as *PSYCHEKS* (Rakús, 1983). The International classification of diseases *(ICD-8* and *ICD-9)* may be mentioned as another of systems which are widely used and generally available.

Studies attempting to specify *DST* for certain type of depressive disorder can be roughly divided into 3 categories: The *first* group of authors ascertains the DST performance for endogenous depression diagnosed according to standard clinical criteria, the *second* group does this for the diagnosis of primary depression according to RDC and the *third* group of investigators (Carroll et al., 1981) for melancholia according to *DSM-III.* Our team ascertains the *DST* performance for the primary depression and so belongs to the second group of investigators. In connection with the search for biological markers of affective disorders a controversy appeared between supporters and opponents of the *DST.* According to Murphy (1981), a laboratory test cannot serve as a confirmation of a psychiatric diagnosis, because the diagnosis is made by identifying the observed symptoms with the described ones, and the *DST* could not a priori belong among the descriptive symptoms. In his reply to the critics B. J. Carroll refers to the usefulness of aminotransferase estimation and ECG evaluation for the diagnosis of heart stroke. He claims that the aim of these studies is not to define a new diagnosis, but to redefine the old one. The critics of the DST further argue, that the probability of the positive test result giving evidence for a diagnosis depends on the prevalence of this diagnosis in the population. The results of Carroll et al. would therefore be valid in population consisting in 58 % of melancholics. One can object that we need the mentioned tool just in such a distorted population, namely the psychiatric one.

Besides PMajDD or melancholia the positive *DST* results are often found in

[1]) in the sense both of "*plus*" and "*minus*".

schizoaffective disorder, in mania (Graham et al., 1982), in anorexia nervosa, alcoholism and dementia (see below).

Degree of actual psychopathology is mostly evaluated using the Hamilton Rating Scale for Depression *(HRSD)* which is used also in our study (Hamilton, 1960). The Brief Psychiatric Rating Scale *(BPRS)*, 100-mm analogue rating scale, subjective scales (Beck or Zung inventory respectively) and others are among further psychometric tools being used on this area. A comprehensive review of this topic is presented in Hanzlíček's (1978) psychiatric encyclopaedia.

METHODS

1. SUBJECTS

Testing psychiatric population among other things for the diagnosis, we did not exclude any psychiatric diagnosis beforehand. The diagnosis of schizoaffective disorder showing often a false positive results of the DST seems to be controversial and there is a possibility, that it is (from this standpoint) a variant of melancholia. See also HANZLÍČEK et al. (1983); see *DSM-III.*

As the main exclusion criteria there remained the circumstances actually or potentially causing the false positive *DST* results, e.g. gravidity, M. Cushing, barbiturate induction of liver enzymes, diabetes mellitus, fevers, epilepsy, hormonal contraceptives, those causing the false negative results of *DST*, e.g. M. Addison, corticosteroid administration, and other endocrine disorders. Deliberately we did not exclude a few alcoholics and all patients treated with psychopharmacological drugs to test the influence of these variables on the *DST* results. Respecting the stated exclusion criteria one should consider the group of psychiatric patients to be representative for the purposes of the estimation of *DST* performance vis à vis the diagnosis of selected affective disorder. Patients may continue their medication provided that it will be well documentated and its influence carefully evaluated. According to our experience (see below) the anxiolytics can be already labeled as a further exclusion criterion for *DST* as they manifestly decrease cortisol blood level after suppression.

The group characteristics: Our group consisted of patients aged from 16 through 69 years, 84 women, 18 men, mean age 39.5 $\pm$13.5 years, 34 out of the total with diagnosis of schizophrenia, 42 with dg. of depression, 6 alcoholics, 11 with other diagnoses and 9 healthy volunteers. The 42 patients with depression include 9 *MinDD* and 33 *MajDD*, 24 out of this number primary and 9 secondary. 24 *PMajDD* consisted of 20 unipolar ones and 4 bipolar *I*. From all depressive patients, 8 were categorized as familial type *I*, 26 as type *II* and 8 as type *III* (for explanation see below). 46 patients were treated with antidepressants, 5 with lithium salts, 66 with neuroleptics, 17 with anxiolytics and 67 with other substances. The mean hospitalization in 69 inpatients lasted 65 days, the average number of hospitalizations was 3.7, maximal 22. The others were outpatients and heatlhy subjects chosen from the staff and medical students.

2. PROCEDURE

1 mg of dexamethasone p.o. is given to the tested person at 11.00—12.00 PM, i.e. at the time of secretion minimum of cortisol. Other employed doses of dexamethasone are 0.5 or 2 mg respectively. The dose of dexamethasone in mentioned range does not seem to influence the performance of the test (Haier and Keitner, 1982), but the dose of 1 mg is very often suggested to be optimal. Blood samples for the estimation of serum cortisol are most frequently taken at 8 AM, 4 PM and 11 PM the following day or even the day before for evaluation of the relative decrease of serum cortisol. The samples

are after separation of the serum stored at the temperature of —20 °C. Simultaneously with the blood samples the saliva is taken. On the first day of the test the persons tested are also examined using psychometric tools (see above), measured and weighted. According to our opinion, the optimal modification of the *DST* in order to economize it and at the same time to keep its performance, is only one blood sample taken at 4 PM after suppression, when as much as 80 % of all positive DST results are stated. In the literature, cortisol levels are usually estimated by competitive binding (Murphy, 1967) and using radioimmunological methods (*RIA*).

3. LABORATORY PROCESSING

We have determined the serum cortisol by *RIA* without extraction (Putz et al., 1981) using low pH (= 4) to reduce the undesired binding on plasma transcortin. Our own rabbit antiserum to cortisol-21-hemisuccinate bovine serumalbumin and overpurified ^{3}H-cortisol fy Radiochemical Centre, Amersham (England) with specific radioactivity 3.96 TBq/mmol as radioligand were used. Adsorption on charcoal with dextran was used to separate free and bound steroids. The determination was made in duplicate. 10 µl of serum was taken for the analysis. Analyses were made on semiautomatic analyzer Labsystem Oy - Finland.

Supposing various suspected advantages (mainly the presence of free cortisol only) we determined by the similar procedure also the saliva cortisol concentrations. In spite of benefits mentioned by Putz et al. (1983), who used also our material, the *DST* performance in saliva is shown to be lower than in serum, which may be related to the fact that the plasma cortisol decrease after dexamethasone is more significant than the decrease of cortisol in saliva. First report on the *DST* in saliva in depressed patients was published by Poland and Rubin (1982).

4. STATISTICS

The *DST* performance is as a rule expressed as sensitivity, specificity and confidence in percent (for example see Carroll et al., 1980). Nevertheless, the *DST* performance expressed in this way may not represent the true validity of the test and becomes often a subject of criticism, mainly for the reason of its dependence on the structure of the population tested, on further variables of various kind (see below), and in addition, such parameter does not indicate the reproducibility of the test etc. Therefore we find it proper to verify the *DST* performance using different (multivariational) statistical methods and finding the *DST* reproducibility etc. Multidimensional linear regression analysis (*MLRA*) seems to be a suitable tool for such estimation. As the regressors, indicators and parameters of considered variables potentially influencing the DST value are used. In the analysis of regression, the regression coefficients of the *DST* (e.g. of serum cortisol levels at 4 PM after suppression) dependence on corresponding regressors and t-tests of significance of these coefficients, are calculated. The hypothesis is tested that the result of *DST* is not in correlation with a regressor and therefore the regression coefficient should be equal to zero. The difference from zero is thus the tested quantity. Unlike in analysis of variance in fully balanced experiments, in the case of *MLRA* the tested regressors are intercorrelated so that the corresponding t-tests represent a verification of partial regression dependences of the analysed result on the corresponding regressors. As a rule, we consider as statistically significant those regressors for which the partial regression coefficients are statistically significant computing all regressors simultaneously. An example of a similar design of *MLRA* see in: Höschl and Roth (1982). Particularly the influences listed below are recommended to enter the analysis arranged in this way.

Reproducibility of the *DST* involves the stability of the results under the stable conditions of the test. According to sporadic preliminary studies the reproducibility of *DST* ranges from 75 % to 89% (Charles et al., 1982; Höschl et al., 1984b). Our preliminary experience shows that the reproducibility of the *DST* in saliva is higher, but with lower performance of the test. This finding can be related to different amounts of free cortisol in different body compartements, as they are in part discussed in: Putz et al. (1983).

RESULTS

We tried to summarize the results of our work, the aim of which is to introduce *DST* into clinical practice, in such an order that they would roughly correspond in both formal and content aspects with the introduction review.

1. *DST* PERFORMANCE FOR THE DIAGNOSIS OF PRIMARY DEPRESSION MADE ACCORDING TO *RDC*

Fig. 1 shows in percent the sensitivity (i.e. the proportion of *PMajDD* patients in whom abnormal *DST* results were found), specificity (i.e. the proportion of *non-PMajDD* subjects in whom normal results were observed) and confidence (refers to the proportion of abnormal test results that were true-positive for *PMajDD*) of *DST* namely in the whole group (n = 102) as well in the subgroup of depressed patients (n = 42). The performance of *DST* in saliva is much lower (Table 1), but the results are more stable when repeated. In the literature we often meet the plasma criterion of suppression of 50 or 60 ng/ml respectively, i.e. 5 resp. 6 μg/l. (Fig. 2) In the preliminary work we evaluated in a small group of patients also the *DST* results obtained at 8 AM and 11 PM. Since *DST* at 8 AM only has low sensitivity and blood sampling at 11 PM is inapropriate for various reasons (disturbing the night rest on the ward, segregation of patients tested, night centrifugation and so on) we have finally chosen (also with regard to economic aspects) so called "outpatient

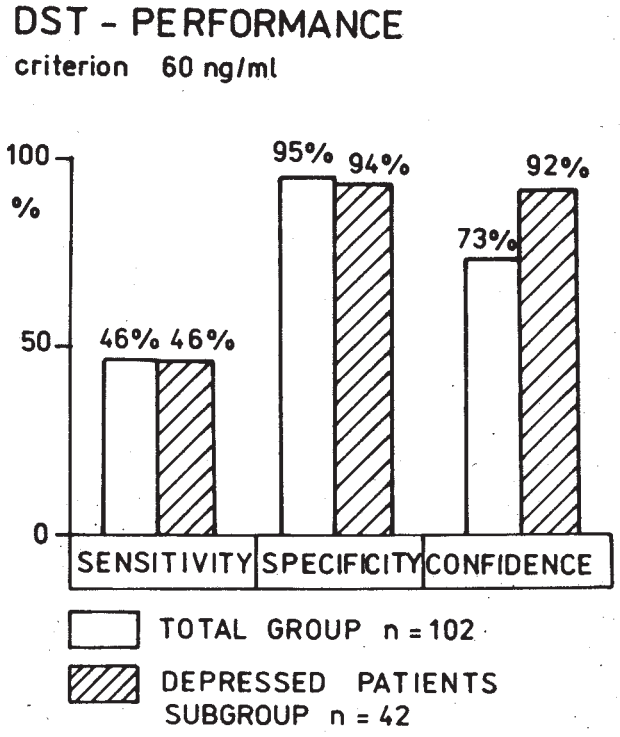

Fig. 1 — Sensitivity, specifity and confidence of *DST*.

Table 1 — *DST* performance — saliva cortisol after suppression (4 PM) (n = 79)

Criterion *(ng/ml)*	Sensitivity *(%)*	Specificity *(%)*	Confidence *(%)*
4	50	54	23
5	33	72	26
6	28	90	45
7	17	95	50
8	17	98	75
9	11	98	67
10	6	98	50

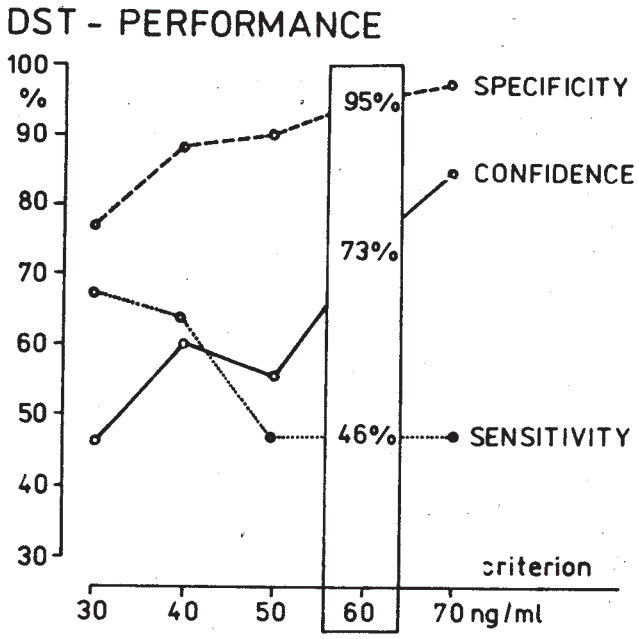

Fig. 2 — The dependence of *DST* performance on the criterion of suppression of cortisol concentration in plasma (ng/ml) in our study.

modification" of *DST*, i.e. blood samples taken only at 4 PM the next day after dexamethasone administration. Ornstová and Jaššová (1983) from our group have shown in their preliminary work that the *DST* performance evaluated from relative decrease of plasma cortisol (before and after suppression) at 4 PM is for *PMajDD* worse than evaluating absolute plasma cortisol levels after suppression. Similarly, the *DST* performance is lower when evaluating differences of the mentioned values. The logarithm of absolute plasma cortisol after suppression correlates most significantly with dg. of *PMajDD*. Basal cortisol levels do not significantly correlate with diagnosis. *DST* is specific also for dg. of *ED* stated according to standard clinical criteria, but only when the influence of *PMajDD*, which supersedes, is not concomitantly evaluated in *MLRA*. Carroll et al. (1981) enhance the sensitivity by also

evaluating at least samples taken at 11 PM as well. These investigators, however, state elsehwere that the sample at 4 PM detects nearly 80 % of positive results. Adding 11 PM samples, one is able to increase only the sensitivity, but the specificity is said to remain unchanged.

2. REPRODUCIBILITY OF DST

The test was repeated twice in a week period with 16 randomly selected subjects (Fig. 3). Taking the more general approach of our study into consideration (see Höschl et al., 1984b), our results are comparable with those of Charles et al. (1982).

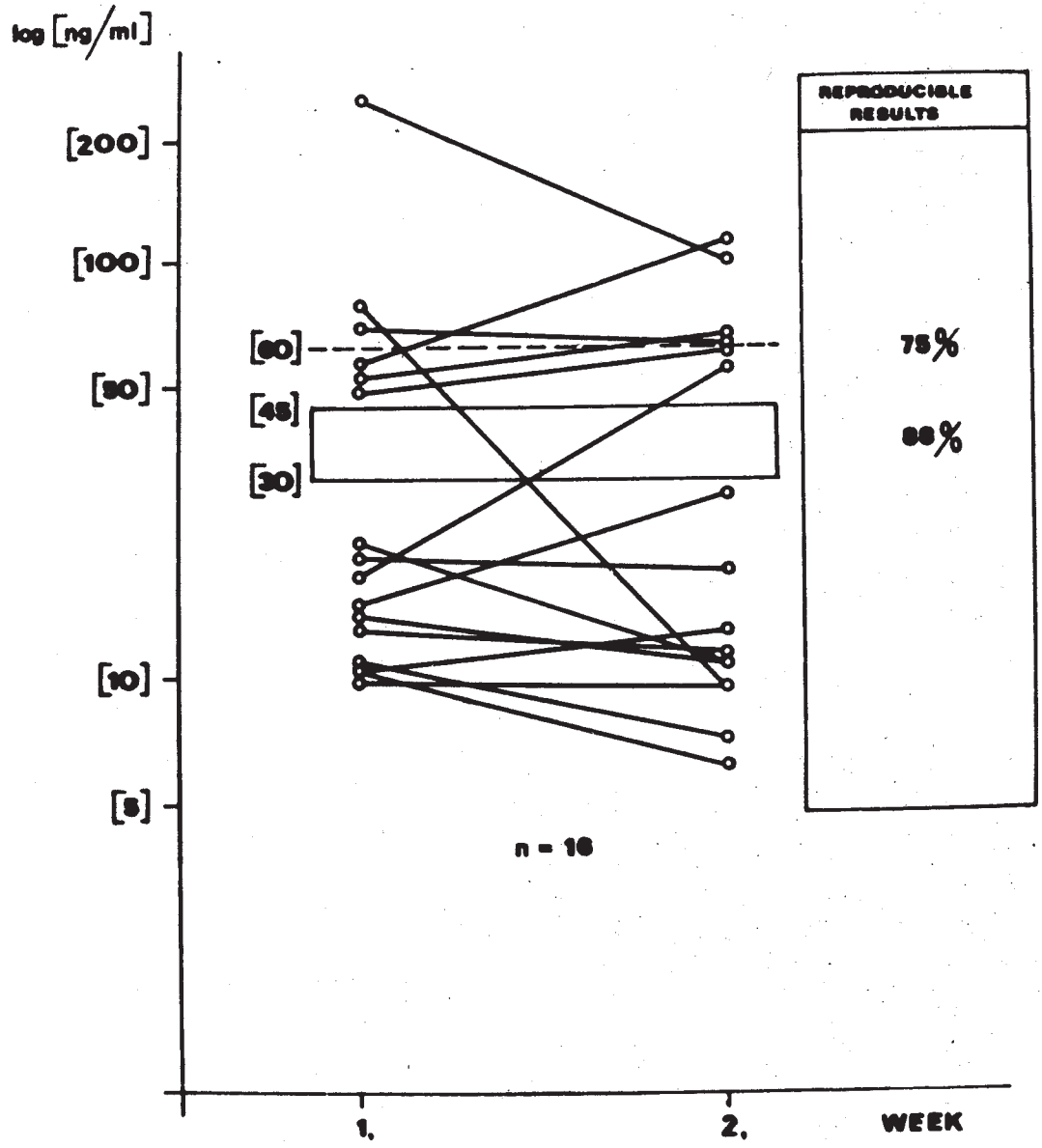

Fig. 3 — Reproducibility of *DST* in a week interval in 16 randomly selected patients. Serum cortisol (*RIA*) at 4.00 PM after suppresion. Reproducibility at criterion 60 ng/ml is 75 % and at 30—35 ng/ml 88 %.

3. SOME INFLUENCES CHANGING DST VALUE

In our previous study (Höschl et al., 1984a) we eliminated the influence of concomitant medication with neuroleptics, tricyclic antidepressants and lithium as nonsignificant. In *MLRA* we therefore retain as important the influence of anxiolytics. (Table 2, Fig. 4, Fig. 5). The different significance of some variables in the Fig. 4 and Fig. 5 respectively may be explained for example by the fact that we omitted the sex because of insufficiently numerous familial types of depressive disorder in the analysis shown at Fig. 4, so that the age gets into prominence.

The effect of alcohol is here evaluated unreliably in the sense that all the 6 patients were chosen only on the basis of a clinical diagnosis of alcohol dependence irrespective of present symptomatology. *DST* has never been administered in ebriety. For these reasons our negative results should be interpreted with great caution. (However, the negative results have been confirmed in our study of about 50 alcoholism; see Höschl et al., *Activ. nerv. sup.*, 27,4 : 277-278)

The deviation from ideal body weight correlates negatively with serum cortisol level after suppression better than simple body weight. Our result is in agreement with some theoretical assumptions discussed below.

Table 2 — An example of multidimensional regression analysis.

Dependent variable: Plasma cortisol level at 4 PM after suppression (average 30.76 ng/l)

Independent variables	*Average*	*Regression coefficient*	*T-test*	*Significance*
Sex (1 = F)	0.805	7.986	1.058	
Age	39.171	0.499	1.989	
Anxiolytics	0.146	—23.134	—2.505	++
Endogenous depression	0.280	—4.315	—0.333	
Schizophrenia	0.366	2.367	0.330	
Alcoholism	0.061	— 2.320	—0.196	
PMajDD (RDC)	0.220	47.141	3.721	+++
No. of hospitalizations	3.660	0.056	0.070	
Psychiatric heredity (1 = yes)	0.329	— 9.433	—1.509	
Somatic complaints	0.305	6.472	0.953	
Index (W—H+100)	2.199	— 0.665	—2.189	+
n = 82 df = 81				

Table shows results in all the group except 20 subjects in whom all data were not completed (e.g. weight or height etc. were not assessed). For further explanation see in text.

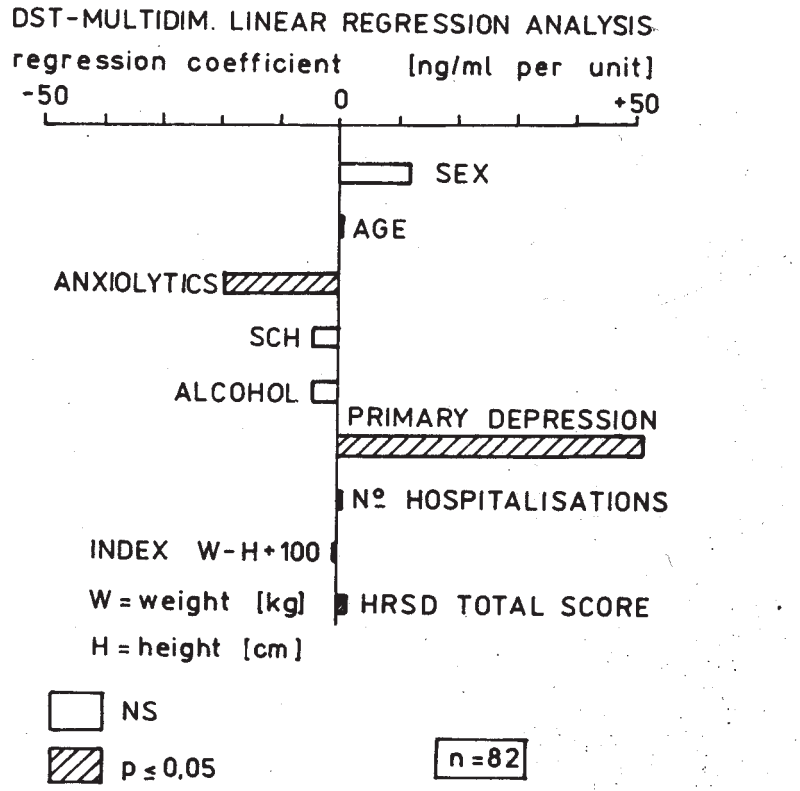

Fig. 4 — Multidimensional linear regression analysis of important variables. Familial types included. (*Sch* — schizophrenia.)

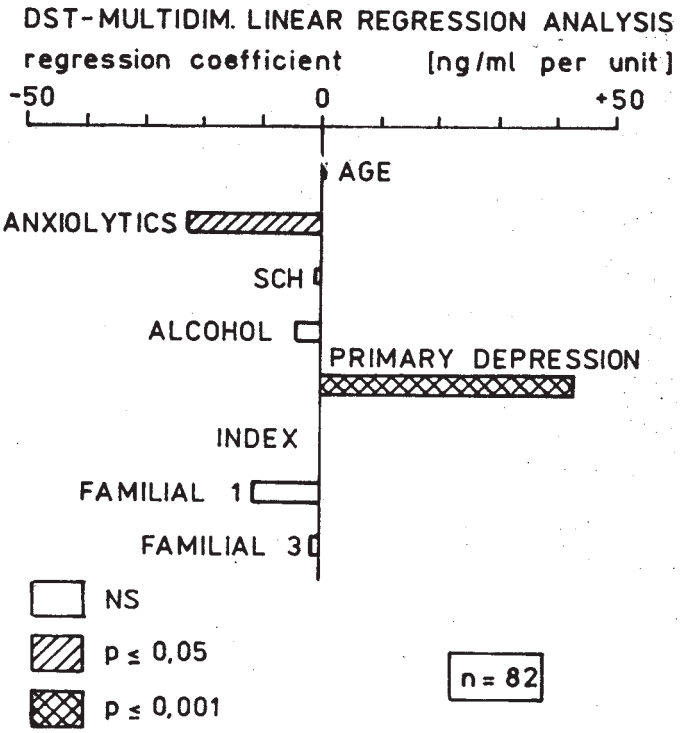

Fig. 5 — Multidimensional linear regression analysis of important variables. Sex included. (*Sch* — schizophrenia, *HRSD* — Hamilton rating scale for depression.)

DISCUSSION

1. SOME INFLUENCES CHANGING THE *DST* VALUE

a) Age

As stated by some reports, geriatric patients (respectively demented ones) with no dg. of *MajDD* show the false-positive results of the *DST*, i.e. early escape from suppression (Spar and Gerner, 1982; Raskind et al., 1982). Other studies (Crumley et al., 1982; Robbins et al., 1982; Poznanski et al., 1982) show that the *DST* performance for *MajDD* in children's or adolescent population is comparable with that in adults. Critical study of Tourigny et al. (1981) does not prove the influence of age alone on the *DST* comparing 10 healthy elderly volunteers and 10 adolescents. The influence of age evaluated using *MLRA* is not significant and does not seem to change decisively the performance of the *DST*, although it shows a similar trend as in the study of Spar and Gerner (1982).

b) Concomitant medication

According to our experience neuroleptics, tricyclic antidepressants and lithium carbonate do not exert influence on *DST*. Regardless of some findings showing increased plasma cortisol after single administration of a butyrophenon, its repeated administration leads to increased tolerance and a normalization of the plasma cortisol (Aimoto et al., 1981). Our findings are also in accord with those of Brown and Shuey (1980). The amphetamine affects doubtless the cortisol secretion (Sachar et al., 1980; Feinberg et al., 1981; Sachar et al., 1981), especially in single pharmacological trials. The patients with endogenous depression seem to react paradoxically by suppression of plasma cortisol approximately one hour after dextroamphetamine administration (Sachar et al., 1981). Psychostimulants, however, do not belong to the usual medicaments in psychiatric practice, which is why we could not evaluate their influence on the *DST* using *MLRA*. With regard to testing carbamazepine as a possible prophylactic agent in affective disorders it is important to note that during the treatment with this agent the false-positive *DST* results may occur (Privitera et al., 1982). In contrast, the benzodiazepines exert an inhibitory effect on the cortisol secretion, especially if the secretion is provoked with stimulants (Butler et al., 1968), which is probably an effect mediated through *GABA*-receptors. Even the inhibitory effect of benzodiazepines on the stress-induced prolactin release in rats is indeed explained in a similar way (Grandison, 1982). *MLRA* also shows a significant inhibitory effect of simultaneous treatment with benzodiazepines on serum cortisol after suppression and therefore on the *DST* result (Höschl et al., 1984a).

The cessation of psychopharmacological treatment just before the *DST* seems to have an unfavorable effect on the *DST* performance (Zapletálek et al., 1982).

c) Alcohol abuse

Alcohol causes an acute plasma corticosteroids elevation in various animal

species (Majumdar et al., 1981; Sturtevant and Sturtevant, 1981; Sturtevant et al., 1981). Oxenkrug (1978) lists the positive *DST* results in alcoholics, even in abstinence. Alcoholism or sporadic alcohol abuse is therefore believed to be a variable which one must either calculate with or exclude alcoholics from the tested group.

d) Heredity

Vinokur et al. (1978) divided the primary depressive disorder along the hereditary taint into three familial types: type *I* - pure depressive disease when the patient has a firstdegree relative with depression, but with no other psychiatric disorder; type *II* - sporadic depressive disease having no firstdegree hereditary taint and type *III* - depression spectrum disease, when alcoholism, antisocial behavior respectively depression (in addition) occurs in first-degree relatives. Schlesser et al., (1980) find the greatest cortisol escape from supression (the positive *DST*) in type I and the lowest in type III. Further studies both confirm (Coryell et al., 1982) and refute (Rudorfer et al., 1982) this finding. *MLRA* does not prove for the time being the significant influence of these types on the *DST* result, but the number of evaluated patients is too small yet to answer this question definitively.

e) Body weight

Though starvation alone apparently does not lead to *DST* positivity, the patients with less than 80 % of the ideal body weight still have markedly frequent elevation of serum cortisol after dexamethasone suppression (Gerner and Gwirtsman, 1981). The patients suffering from anorexia nervosa do not seem to have a longer biological halftime of dexamethasone. Rather the depressed inhibitory action of noradrenergic fibres on *CRH* secretion is considered as low urinary *MHPG* (indicator of norepinephrine turnover) is often found in these patients. These findings along with some genetic studies turn the attention to possible relationship between anorexia nervosa and primary depression (Gwirtsman and Gerner, 1981). Somewhat different results are presented in the study showing that even the strict reducing (with the weight loss greater than 1.5 kg weekly) diet may result in positive *DST* (Berger et al., 1982). For these reasons we regard the body weight or index showing the deviation from ideal body weight (weight-height + 100) as an important variable entering *MLRA*.

f) The influence of pain

Blumer et al. (1982) found some positive "biological markers" of depression including the *DST* in patients with chronic psychogenic pains and they conclude that disorders with tendency to otherwise inexplicable pain can be regarded as a variant of depressive disorder. However, other authors (Lascelles et al., 1973) suggest higher plasma cortisol both in psychogenic pains and (especially!) in those of organic origin, the difference between them being only quantitative. In view of the fact that pain may be a part of the depression syndrome (see the diagnostics above) and also that the fine differential diagnosis of pains stays almost out of psychiatric possibilities it is not possible for the time being to evaluate such variable independently in *MLRA*.

g) Stress

Though the problem of stress is somewhat confused at the moment, stress is in general supposed to be a state of organisms in which the *ACTH* secretion is increased. However, the very findings in affective disorders noted above rather challenge this definition. That is to say, it seems that the increased productivity of *HPA*-axis in endogenous or primary depression is not explicable by stress as a psychogenic load (distress) (Curtis, 1976). The patients with other diagnoses (e.g. schizophrenics), being generally faced with the same stressors (including the blood puncture) during their psychiatric hospitalization, do not show the *DST* positivity. The overestimation of the influence of a momentary stress on the DST performance is to be rejected. Studies occur which show significant differences between the *DST* results in *PMajDD* and in anxiety states diagnosed in the local framework as neurosis but in *DSM-III* as "panic attack" (Curtis et al., 1982; Sheehan et al., 1983).

h) Sleep

The relation between shortened *REM*-latency in depression and *DST* positivity is not clear. Nonsuppressors (= *DST* positive) seem to react better on sleep deprivation therapy (Nasrallah and Coryell, 1982; King et al., 1982).

Some other influences concerning the DST were discussed above.

2. HPA-AXIS REGULATION IN DEPRESSION

The increased productivity of *HPA*-axis in some depression disorders used to be explained by depressed inhibitory action of noradrenergic neurons from eminentia mediana of hypothalamus and other limbic centers (Collu, 1977). The changed plasmatic cortisol binding in depressed patients was also considered (King, 1975), but this does not seem to be the cause of *DST* positivity. Also the metabolism of dexamethasone, the higher clearance of which could explain the early escape from suppression, is not changed in depression. The relative cholinergic superiority in depression, which leads perhaps to desensibilisation of central parts of *HPA*-axis to the negative feedback influence of given corticosteroid, may be a further possibility of explanation. Sporadic studies (Carroll et al., 1978) indeed show that positivity of *DST* in normal subjects after physostigmine administration can be found. Some other authors, however, explain this phenomenon by distress following the physostigmine administration. Meltzer et al. (1982) suggest nevertheless pituitary cause of *DST* positivity in depression rather than the dysregulation of the limbic system, arguing that dexamethasone significantly depresses also the prolactin level and the excape from the "prolactine suppression" correlates significantly with the escape from suppression of cortisol in depressed patients although both hormones are subjected to different central monoaminergic regulating structures.

Some investigators (Holsboer et al., 1983) suppose that the enhanced hypothalamo-pictuitary activity plays perhaps a causal role in the development of depressive disorder since steroids affect beta-adrenergic function, density of receptors

etc. In spite of this, the causes of *DST* positivity in depression, are, so far, far from being clear. (See also Höschl, C.: *Zprávy VÚPS*, No. 73, Praha 1986, in Czech)

3. PREDICTIVE VALUE OF THE DST

Taking into account the reproducibility of *DST*, the test shows certain predictive ability in the sense that its change precedes the change of a clinical picture in transition from the remission to the phase and back (Greden et al., 1980; Holsboer et al., 1983).

CONCLUSIONS

The present study of *DST* performance for dg. *PMajDD* and the evaluation of potentially intervening variables imply that:

1. DST in the presented modification shows relatively low sensitivity (46 %) for *PMajDD* but is more economical (almost twice if compared with the test using two blood samples).

2. DST is highly specific for *PMajDD* (95 %), even in our modification.

3. DST is believed to be relatively reliable (73 % confidence) for the determination of the dg. *PMajDD*, both in the framework of differential diagnostics of depressions and in larger psychiatric populations.

4. Reproducibility of *DST* seems to be higher than 50 %. It is, however, necessary to verify this in further investigations.

5. The overall performance of *DST* is shown to be comparable with other laboratory tests currently used for example in internal medicine, such as the estimation of transaminase for the diagnosis of heart-stroke, or *ECG* for heart disorders, etc. (cit. Carroll et al., 1980).

6. It is not necessary to stop medication before the test, but the significant negative effect of anxiolytics on serum cortisol after suppression (patients with anxiolytics show walues about 20 ng/ml lower) has to be taken into account.

7. DST result depends on the degree of actual depression expressed by the total score of *HRSD* only to the extent that the patients in the phase of primary depression show higher total scores than others and have more often abnormal *DST*. The *DST* result apparently reflects longer-term state of the actual degree of psychopathology.

8. Marked deviation from ideal body weight correlates negatively with the serum cortisol level after suppression.

9. DST on saliva shows much lower performance for *PMajDD*, but is suspected to have better reproduciblity.

10. DST in presented modification seems to be a suitable tool for differential diagnostics, in psychopharmacological research, perspectively even for forensic purposes etc.

APPENDIX

The following points are related to international recommendations for publications concerning depressive disorder as they were published in *Psychopharmacol. Bull.*, 19, 1983, 2, p. 162—164:

A — Methodological issues

ad *1.* Results obtained in presented group of patients were partly published in the proceedings of a student's university conference (Ornstová and Jaššová, 1983) and in the proceedings of 25th psychopharmacological conference in Lázně Jeseník, January 1983 (Höschl et al., 1984 a, b).

ad *2.* The research team was blind with respect to ward staff and vice versa, so that the diagnosis according to *RDC* was determined independently on the ward clinical diagnosis. The laboratory *(Endocrinological Research Institute)* was completely "blind" towards the hospital and therefore towards the group of patients. The laboratory was not informed as to how many patients the delivered blood samples belong and whether they are not only control samples. Laboratory processing, clinics and research arrangement are therefore independent on each other. The statistician (Z. Roth, PhD. from *Institute of Hygiene and Epidemiology*, Prague) was completely "blind" and independent with regard to the laboratory and clinics, and he was not aware of the theoretical assumptions of the study.

ad *3.* The subjects tested were chosen from inpatients or outpatients of *Mental hospital in Prague-Bohnice*, wards No. 27, 23 and 19. Healthy volunteers were recruited from among the staff (nurses) and medical students.

ad *4.* Two persons were excluded for technical reasons (broken test tube, accident during laboratory processing) and one woman was excluded for ex post found hormonal contraception.

ad *5.* Exclusion criteria are listed in the text.

ad *6.* The diagnosis was made by two university medical students — research assistants — under the guidance of an assistant professor, based on 2 interviews and on former case documentation. No other independent diagnosis according to *RDC* was determined. Current clinical diagnosis was estimated by ward doctors independent on the study.

B — *Variables describing the group of patients are listed both in the text and in Table 2.*

SUMMARY

102 subjects underwent the *DST*. 34 out of them were schizophrenics, 42 suffered from depression (24 out of this number had primary major depressive disorder), 6 alcoholics, 11 with other diagnosis and 9 healthy volunteers. 1 mg of dexamethasone p.o. was given at 11.30 PM. Blood samples for *RIA* of serum cortisol were taken at 4 PM the following day. The dependence of serum cortisol level after suppression on variables (e.g. age, sex, medication, diagnosis etc.) was evaluated using multidimensional linear regression analysis. The serum cortisol level 60 ng/ml after suppression was chosen as the criterion of suppression. *DST* shows 46 % sensitivity for primary depression, 95 % specificity and 73 % confidence. Reproducibility of *DST* seems to be higher than 50 %. Anxiolytics have significant negative effect on serum cortisol level after suppression. Marked deviation from ideal body weight correlates negatively with the serum cortisol after suppression. In addition, some other aspects of *DST* including *DST* on saliva etc. are mentioned in the paper.

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