Amy S. F. Lutz: The Rise and Fall of the Dexamethasone Suppression Test: Stability, Consensus, Closure

Martin M. Schumacher's Comment

> *Science is a way to teach how something gets to be known, what is not known, to what extent things are known (for nothing is known absolutely), how to think about things so that judgments can be made, how to distinguish truth from fraud, and from show.*
>
> Richard Feynman (American physicist and Nobel laureate, 1918 – 1988)

Introduction

Amy Lutz's thoughtful and informative paper, *The Rise and Fall of the Dexamethasone Suppression Test: Stability, Consensus, Closure,* (Lutz 2021) is a timely reminder of the largely forgotten subject of endocrine psychiatry, the dexamethasone suppression test (DST) being its most prominent representative and is therefore very welcome. But why should we care about a dead fish in psychiatry's waste bucket? Indeed, there was a time when hormones were very much at the center of psychiatry's interest and the DST a subject which caused much enthusiasm and high expectations. But alas, this is a thing of the past.

Many, if not most, younger psychiatrists won't have even heard about the DST and will probably not consider endocrinology to be of much relevance to their clinical work with real patients. Those young (or older) psychiatrists who are nevertheless interested in the value of the DST in psychiatry, might turn to the latest edition of *Kaplan and Sadock's Comprehensive Textbook of Psychiatry* (Sadock, Sadock and Ruiz 2017) for guidance. There we read on page 1608, "This procedure (i.e., the DST) is of uncertain specificity for depressive illness and, thus, is unsuitable to serve as a diagnostic test." We doubt that this harsh judgement is warranted and will argue in this contribution that the DST should be reconsidered, improved, properly standardized and validated. Thereafter, the DST will be a useful tool for the diagnosis and dissection of mood disorders, for the identification of homogeneous patient populations needed for a successful drug development, and other purposes.

When it comes to a close study of the DST and its application in psychiatry, we are chartering deep water. The DST is at the intersection of psychiatric nosology, psychopathology, endocrinology, clinical chemistry and statistics. Bernard J Carroll (1940-2018), the man who introduced this test in psychiatry, had a good understanding of most of the disciplines listed above. Obviously, not everybody who worked in this field and applied the DST had the same

standing and might have only added to the confusion and the subsequent fall from grace of the DST.

Another important person making important contributions to the field of endocrine psychiatry was Edward J. Sachar (1933-1954). Sachar was a little older than Carroll and we believe that he would have made more essential contributions to endocrine psychiatry and to the controversy about the DST, if not a stroke in 1981 (which ended his academic career) and his untimely death in 1984 would have prevented this. His interests and findings are reflected in numerous publications and several books (Sachar 1975, 1976a,c; Sachar, Roffwarg and Gruen 1976b; Halbreich 1987).

Hormones were the firstborn of biological psychiatry (Duval 2003). However, with the advent of neuroleptics and antidepressants in the 1950s and 1960s and the subsequent formulation of the serotonin/norepinephrine and dopamine theories of depression and schizophrenia, respectively, the interest of psychiatry in hormones declined dramatically and shifted to neurotransmitters. For the last four decades, most of the research activities of biological psychiatry and the development of psychotropic drugs were focused on no more than a handful of neurotransmitters. What are the fruits of this focus after 40 years of hard labor and the investment of billions of dollars? Alas, very little.

After the introduction of the first wave of modern psychotropics (e.g., chlorpromazine, imipramine, meprobamate and chlordiazepoxide) a plethora of me-too drugs was developed. No real innovation happened in all those years. The claims of superiority of newer drugs (e.g., the SSRIs and the "atypical" neuroleptics) did not stand the test of time. Moreover, the serotonin/norepinephrine and dopamine theories mentioned above are now largely abandoned.

Psychiatry as a discipline is in trouble. The disorders in its *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) are mostly not validated (Kendler 2016) and the efficacy of its drugs limited (Shorter 2021). It is obvious that a neurotransmitter-focused psychiatry regarding both etiology/pathophysiology and pharmacotherapy of mental disorders has reached a dead end. The current hot topics with regard to psychotropic drugs are the old dissociative compound ketamine (first synthesized in 1962) and the hallucinogen psilocybin, which has been used for millennia by shamans. The *decade of the brain* in the 1990s brought a lot of excitement, but only little lasting value for clinical psychiatry. It seems that contemporary psychiatry is in a desperado mode, not knowing in which direction to advance nor where to find solid ground.

The author believes that it's time to reconsider a more comprehensive psychiatry. Proponents of different psychiatric schools have rightly lamented a "brain-less" psychiatry, others, more recently, a "mind/soul-less" psychiatry. However, there is more to a human being than the brain and the mind. In 1857 Bucknell, considered by some to be the father of British psychiatry, wrote that three different theories of insanity can be distinguished: the somatic, the psychic and the somato-psychic (Lipowski 1986, 1990). The somatic (biological) theory, being currently the most popular one, reduces normal mental processes and psychopathology to the brain and its neurochemistry. The psychic theory (i.e., psychoanalysis) dominated psychiatry in the US from the end of World War II until the 1970s. The somato-psychic theory calls for a more integrative approach to mental disorders, including the whole body (most of the endocrine glands do not belong to the brain).

Diseases of many organs are associated with psychiatric symptoms. The human nervous, immune and endocrine systems are intimately interconnected and a dysfunction of any of them can have an impact on mental health. As mentioned above, the nervous system already received a lot of attention since the introduction of the first neuroleptic and antidepressant drugs. In 2007, the Spanish neurologist Josep Dalmau and colleagues published the case of a patient with psychiatric and neurological symptoms. They identified an encephalitis caused by N-methyl-D-aspartate (NMDA) receptor autoantibodies (Sansing, Tüzün, Ko et al. 2007). Often autoimmune encephalitides at first cause only psychiatric symptoms without any neurological signs. These findings precipitated a lot of very fruitful research in the field of psychoneuroimmunology (Bullmore 2018; Dalmau, Armangué, Planagumà et al. 2019; Pollak, Lennox, Müller et al. 2020) which is still ongoing. However, the study of the relationship between the endocrine system and mental disorders (psychoendocrinology/endocrine psychiatry) fared less well. Although a lot of basic research has been done in this field, the impact on the clinical practice of psychiatry is still very limited.

Edward Shorter and Max Fink, in their 2010 book *Endocrine Psychiatry*, give a very informed introduction into the history of the field and in particular a detailed description of the rise and fall of the DST. Their book makes enjoyable reading and the interviews with many of the key actors in the DST controversy add a lot to the understanding of the different forces at work and the causes of its final fall from grace. Anybody interested in a comprehensive overview is encouraged to study this book or at least a more recent abbreviated publication of Shorter (2020). Amy Lutz's paper adds important new material and additional perspectives to our subject. Based on this foundation, it is not an easy task to contribute something new. However, we believe that there are more aspects and facts to be considered, and we shall add our two pence, hoping that one or the other point in this comment will trigger a fruitful discussion.

Hypercortisolism, the HPA-axis, and depression

Hypercortisolism is a common observation in patients with severe depression (Sachar 1976a; Sachar, Roffwarg, Gruen et al. 1976b; Carroll, Curtis, Davis et al. 1976a; Carroll, Curtis and Mendels 1976b) which manifests itself in elevated levels of cortisol in serum, CSF (cerebrospinal fluid), saliva and/or 24-h urine and elevated levels of CRH (corticotropin-releasing hormone) in CSF. Work started in the 1960s (Sachar 1967; Carroll, Martin and Davies 1968) and recently a comprehensive review was published (Nandam, Brazel, Zhou and Jhaveri 2020).

An example of elevated levels of cortisol and a somewhat blurred diurnal rhythm in depressed patients is shown in Figure 1.

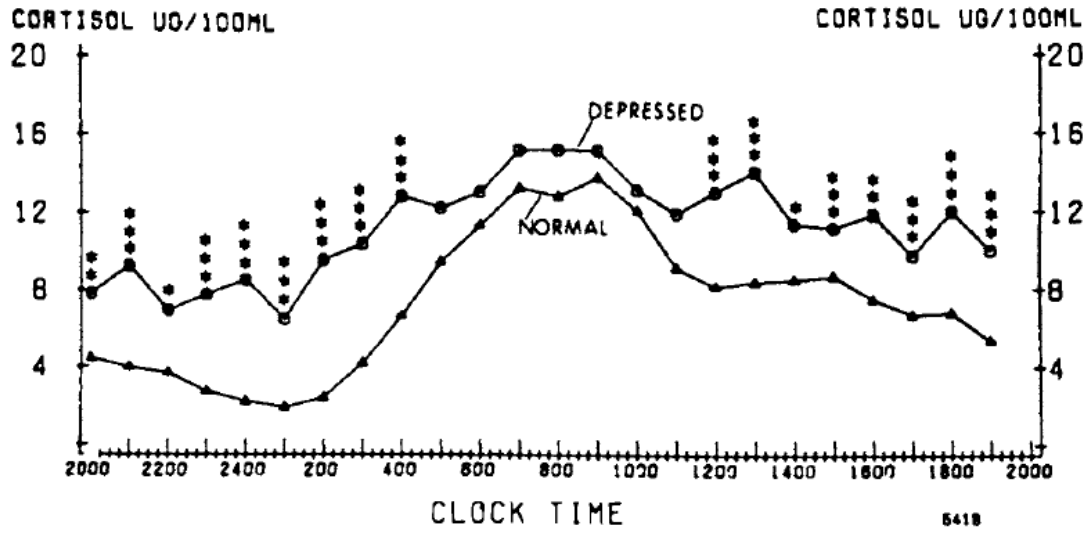

Figure 1. Circadian mean levels of cortisol in depressed patients and normal controls (cortisol concentrations in µg/dl) (Sachar 1976c).

On the other hand, depression, and to a lesser extent mania and anxiety, is also very common in patients suffering from Cushing's syndrome (CS) (Condren and Thakore 2001; Sonino and Fava 2001). A detailed list of the different etiologies of CS is shown in Table 1.

I. Endogenous
1. Pituitary-dependent, ACTH-mediated (Cushing's Disease)
a. Microadenoma of the anterior lobe
b. Macroadenoma of the anterior lobe
c. Hyperplasia of corticotropes
d. Tumors of the intermediate lobe
2. Tumors of the adrenal cortex
a. Adenoma
Single
Multiple
b. Carcinoma
3. Nodular hyperplasia
a. Micronodular disease
b. Macronodular disease
c. Primary adrenocortical nodular dysplasia (PAND)
4. Ectopic ACTH syndrome
a. Ectopic secretion of ACTH
b. Ectopic secretion of CRH
II. Exogenous
1. Iatrogenic
2. Factitious

Table 1. The etiologies of Cushing's syndrome (hypercortisolism) (Kannan 1988).

A specific subtype of CS, namely the one caused by a tumor of the pituitary, is called Cushing's disease (CD). CD was first described by the American neurosurgeon Harvey Cushing (1869 –1939), who noted and was keenly interested in the accessory neuropsychiatric symptoms (Cushing 1913, 1932). In the majority of the patients with CS, the hypercortisolism is due to hypersecretion of the adrenocorticotropic hormone (ACTH) by a pituitary tumor, ectopic ACTH secretion from an extrapituitary neoplastic lesion or to autonomous cortisol secretion by an adrenal tumor. All the endogenous etiologies listed in Table 1 can be confirmed by imaging techniques (e.g., computed tomography [CT], magnetic resonance tomography [MRT]) and/or the histopathology of tissue obtained by a biopsy.

The CS patients with an *exogenous* etiology fall into two different groups. The group with an *iatrogenic* cause is that with CS due to a prolonged treatment with corticosteroids or ACTH. The group of exogenous CS called in Table 1 *factitious* is usually called *Pseudo-Cushing's syndrome* (i.e., physiologic or non-neoplastic CS). The most common causes of pseudo-Cushing's syndrome are neuropsychiatric disorders, polycystic ovary syndrome (PCOS), obesity, poorly controlled diabetes mellitus, alcoholism and eating disorders (Scaroni, Albiger, Palmieri et al. 2020). All these different endogenous and exogenous etiologies of CS have an excessive secretion of cortisol as a common final pathway. The clinical pictures with regard to the physical and mental signs and symptoms are due to the underlying hypercortisolism and do not allow for an identification of their etiology.

The distinction between endogenous and exogenous CS can be a challenge for both the endocrinologist and the psychiatrist and might result in a wrong diagnosis with all its ill consequences for the patient. This situation becomes even more complicated as some patients having physiological hypercortisolism exhibit only minimal physical features of Cushing's syndrome. Also, subclinical forms of endogenous Cushing's syndrome (Tsagarakis, Vassiliadi and Thalassinos 2006; De Leo, Cozzolino, Colao et al. 2012) exist, with psychiatric symptoms as their first and only manifestation (Lacroix, Feelders, Stratakis et al. 2015). A recurrent form of CS, "Cyclical Cushing's syndrome," has been reported for all etiologies of the syndrome. Irrespective of age, primary pigmented nodular adrenocortical disease (PPNAD) and isolated micronodular adrenocortical disease are also often cyclic (Lacroix, Feelders, Stratakis et al. 2015). This form can closely mimic recurrent mood disorders like melancholia.

Treatment of CS should target the underlying etiology. Iatrogenic CS and the mental symptoms caused by prolonged treatment with glucocorticoids (Ricoux, Guitteny-Collas, Sauvaget et al. 2013) will dissolve when the drug is withdrawn (in a challenge/re-challenge manner, indicating causality). Reduction of glucocorticoid synthesis or action, either with metyrapone, ketoconazole or mifepristone, rather than treatment with antidepressant drugs, is generally successful in relieving depressive symptoms, as well as other disabling symptoms (Murphy 1991, 1997). Following successful surgical treatment of hypercortisolism, both physical and psychiatric signs and symptoms improve substantially (Pereira, Tiemensma and Romijn 2010). These findings suggest that hypercortisolism might be the cause of the observed psychopathology.

Dexamethasone (DEX) is a synthetic high-potency glucocorticoid with a long biological half-life. It is about 25 times more active than endogenous cortisol. When given to a healthy subject, it acts on the hypothalamus and pituitary and suppresses the secretion of cortisol. In patients with Cushing's syndrome, this suppression does not take place. Figure 2

shows schematic presentations of the *Hypothalamic–Pituitary–Adrenal* (HPA) axis for a healthy (normal) individual and a patient with Cushing's disease, with and without the action of DEX. The activity of the HPA axis is determined by corticotropin-releasing hormone (CRH), adrenocorticotropic hormone/corticotropin (ACTH) and cortisol. In a healthy subject, the release of CRH and ACTH is regulated by cortisol via a negative feedback mechanism. In CD and other subtypes of CS this feedback is impaired, leading to the secretion of excess cortisol.

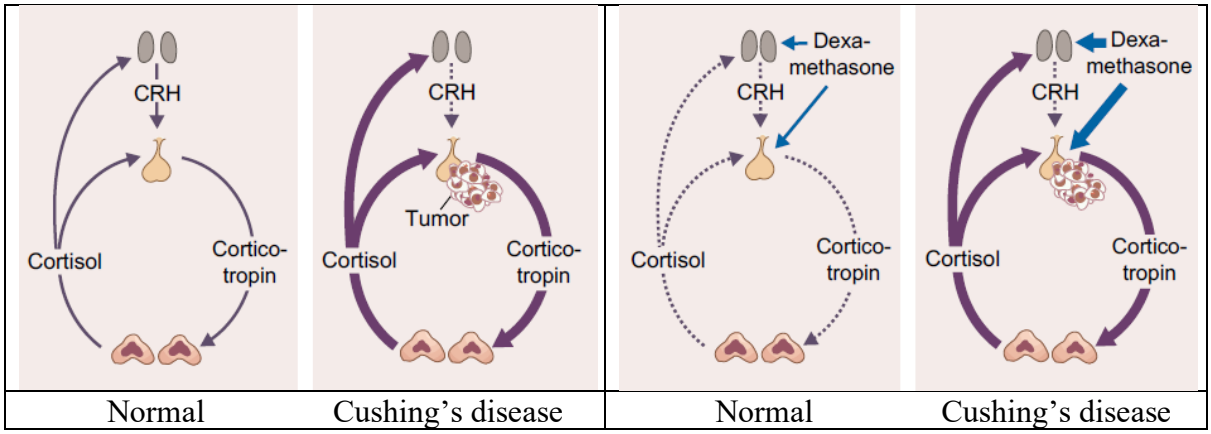

Figure 2. Physiologic and pathophysiologic features of the Hypothalamic–Pituitary–Adrenal (HPA) axis in normal subjects and patients with Cushing's disease (left panel) and the effect of dexamethasone (right panel). Solid lines indicate normal, dotted lines suppressed and fat lines overactivity of the HPA-related hormones CRH, ACTH and cortisol (Orth 1995).

The DST as used in endocrinology and psychiatry for the assessment of the functionality of the HPA axis, works by the acting of the dexamethasone on the hypothalamus and the pituitary. In healthy subjects (2nd picture from the right in Figure 2) dexamethasone causes a suppression of cortisol secretion. In endogenous (neoplastic) CS this suppression does not take place (1st picture from the right in Figure 2).

Interestingly, in some patients with exogenous CS (Pseudo-Cushing's syndrome) subjected to the DST a non-suppression is also observed. This was the motivation for the use of the DST for the diagnosis of melancholia, which an endocrinologist considers belonging to the group of Pseudo-CS, and at the same time the findings stated in this section indicate other causes of false-positive findings (i.e., non-suppression) and the need for a differential diagnosis (i.e., exclusion of endogenous/neoplastic CS).

The psychiatric symptoms and their frequency observed in patients with endogenous CS and those with major depression are listed in Table 3.

Symptom:	Cushing's syndrome (%)	Major depression (%)	
No. of patients:	35	54	95
Ref.:	[24]	[7]	[6]
Depressed mood, feeling sad	74	93	93
Increased fatigue	100	57	NR[a]
Decreased energy	97	NR	75
Decreased libido	69	50	50
Irritability	86	67	NR
Crying	63	50	NR
Restlessness	60	59	46
Anxiety, apprehensiveness	66	30	NR
Impaired memory	83	NR	NR
Impaired concentration	66	93	76
Early insomnia	29	59	64
Middle insomnia	69	46	67
Late insomnia	57	61	58
Social withdrawal	46	NR	NR
Hopelessness	43	61	95
Guilt	37	28	31
Increased appetite or weight gain	34	7	NR
Decreased appetite	20	87	52
Slowing thoughts	11	69	NR
Thought blocking	17	NR	NR
Speeding thoughts	14	NR	NR
Elation-hyperactivity	11	NR	NR
Perceptual distortions, delusions	11	11	NR
Paranoid thoughts	9	7	9
Suicidal attempts	10	11	NR

Table 3. Frequency of psychiatric symptoms in patients with Cushing's syndrome and patients with major depression (NR: not recorded) (Murphy 1991).

Obviously, there is a substantial overlap of symptoms, but the psychopathological pictures are not identical. Biochemically, CS and major depression differ in at least four respects: ACTH level, CRH level, glucocorticoid number and response of ACTH to CRH (Murphy 1991). The common denominator of the two conditions is hypercortisolism. Endocrinologists have made great efforts to differentiate between endogenous and exogenous CS, and to understand the etiologies/pathophysiologies of Pseudo-Cushing's syndrome, including neuropsychiatric cases, better (Lindholm 2014). The author believes that psychiatry could gain a lot by a close collaboration with endocrinology.

The dexamethasone suppression test (DST) as proposed by Carroll and colleagues

In 1981 Carroll, together with 11 colleagues from the University of Michigan at Ann Arbor, published the groundbreaking article, "A specific laboratory test for the diagnosis of melancholia. Standardization, validation, and clinical utility" in the *Archives of General Psychiatry* (Carroll, Feinberg, Greden et al. 1981). According to Google Scholar this article was cited 2,433 times until March 2022.

A total of 368 patients (180 inpatients, 188 outpatients; 215 patients with a diagnosis of melancholia, 153 patients with a diagnosis of non-melancholic depression or other mental

disorders) were studied. Additionally, 70 normal subjects were subjected to the DST for reference purposes.

To put our discussion of the DST on a solid foundation, let's first have a look at the definition of the parameters of the test, findings, claims and limitations, as stated in this reference.

Test parameters

- Dose and timing of dexamethasone (DEX): 1 mg p.o. at 11 pm
- Two blood samples taken at 4 and 11 pm after administration of DEX for the quantification of cortisol
- Non-suppression defined by a cortisol concentration >5 μg/dl at any of the two time points
- Quantification of plasma cortisol by the *competitive protein binding method*
- Patients with specific somatic diseases should not be subjected to the test
- Diagnosis of melancholia by a composite clinical assessment (Carroll, Feinberg, Greden et al. 1980; see also the section "Nosological aspects" below)

Results

- The DST identifies melancholic inpatients with a sensitivity of 67% and a specificity of 96% (for melancholic outpatients a sensitivity of 49% was obtained)
- Outcome of the DST is not related to age, gender or recent use of psychotropic medication
- The impact of the severity of depressive symptoms (according to the HDRS) on the outcome of the DST was not investigated
- In patients with a psychiatric diagnosis other than melancholia and in normal subjects the specificity of the DST was in both cases 96%
- Nocturnal (11.30 pm) pre-DEX plasma cortisol levels had less diagnostic power (i.e., lower sensitivity and specificity) than the DST
- The group of melancholic patients is heterogeneous with respect to neuroendocrine function as assessed by the DST
- A negative DST result does *not* rule out the diagnosis of melancholia
- Some medical disorders and drugs leading to false-positive or false-negative test results are listed (9% of all outpatients and 20% of all inpatients from the study were excluded for medical reasons)
- Abnormal DST responses (i.e., non-suppression) return to normal upon recovery of the condition

One year later Carroll published a review of the DST in the *British Journal of Psychiatry* (Carroll 1982). In this comprehensive review results obtained by different groups are summarized and compared to his own findings. Different clinical uses of the DST and applications to nosology are discussed (see also: Carroll 1984).

Results

- Sources of variation in sensitivity (DEX dose, post-DEX schedule/timing of blood sampling, post-DEX plasma cortisol threshold, diagnostic criteria) are discussed
- Definition of the DST: *The DST is a specific episode-related biological marker of melancholia (*i.e., the DST is a state-dependent biomarker, not a trait marker of melancholia per se)
- Clinical uses: Assessment of treatment response to ECT or pharmacotherapy with TCAs, prediction of relapse, indicator of suicide risk
- The diagnostic confidence of the DST depends on the prevalence of cases (i.e., patients with melancholia). Therefore, the DST is not suitable in situations with low prevalence, i.e., for screening purposes in a general outpatient setting (Shapiro and Lehman1983).

The DST in the hands of other researchers

How does one validate a biological marker of endogenous depression when a valid clinical definition does not exist?
Mark Zimmerman (Zimmerman, Coryell and Pfohl 1986a)

What is both impressive and dismaying in reviewing the published DST evaluations is that there is not one DST, but almost as many DSTs as there are DST studies. Mixing together different tests is a major source of the confusion in the evaluation of the DST, particularly in the reviews of the test.
Helena Kraemer (Kraemer 1987)

A modified dexamethasone suppression test (DST) has had unprecedented evaluation among biologic tests proposed for clinical use in psychiatry. It has not proved to reflect pathophysiologic changes at the level of the central nervous system or pituitary, and tissue availability of dexamethasone itself may contribute to test outcome.
George Arana (Arana, Baldessarini and Ornsteen 1985)

The DST has been applied by many research groups and resulted in a large number of publications in peer-reviewed journals. The results are of a very heterogeneous and even contradictory nature. We will make no attempt to review all these papers. The interested reader is referred to the 2010 book of Shorter and Fink and the 2021 paper of Lutz for more details. Although the majority of publications report a significantly elevated proportion of non-suppression in depressed patients with melancholic features, the sensitivities are usually lower than the 67% reported by Carroll and cover a broad range. Also, the proportions of non-suppressors in patient populations with psychiatric diagnoses apart from melancholia and even normal controls is often substantially larger than the 4% reported by Carroll (specificity = 96%). There are several comprehensive reviews available (Green and Kane 1983; Shapiro and Lehman 1983; Meltzer and Fang1983; Coryell 1984; Arana, Baldessarini and Ornsteen 1985; Krishnan, Davidson, Rayasam et al. 1987; Arana and Mossman 1988; Rush, Giles, Schlesser et al. 1996).

Table 2 shows the DST results of several research groups based on the *Research Diagnostic Criteria (RDC)* criteria for the definition of MDD-ET (major depressive disorder - endogenous type). Different test parameters, as shown in the table, were used. The proportion

of non-suppressors with MDD-ET covers the range of 22 to 81% (mean = 40%). For control subjects the proportion of non-suppressors is 4-15% (mean = 10%) and for patients with other psychiatric illnesses 0-37% (mean = 18%).

			Sensitivity for MDD			Specificity					
			MDD patients			Control subjects			Other patients with psychiatric illness		
				Nonsup-pressors			Suppressors			Suppressors	
Study	Dose (mg)	Sampling time	Total N	N	%	Total N	N	%	Total N	N	%
Stokes et al (12)	1	8 a.m.	74	19	26	70	63	90	27	17	63
Coppen et al (13)	1	4 p.m.	78	63	81	79	70	89	232	151	65
Carroll et al (14)	1	4 p.m.	51	18	35	70	67	96			
Carroll et al (1)	1+2	8 a.m., 4 p.m., 11 p.m.							153	147	96
Amsterdam et al (15)	1	4 p.m.	64	16	25	53	45	85			
Schlesser et al (16)	1	8 a.m.	86	37	43				80	80	100
Brown et al (17)	2	8 a.m., 4 p.m., 11:30 p.m.	20	8	40				29	29	100
Holsboer et al (18)	2	4 p.m.	74	16	22				28	24	86
Total			447	177	40	272	245	90	549	448	82

Table 2. DST identification of major depressive disorder (MDD), endogenous type, according to *RDC* (Insel and Goodwin 1983).

In Table 3 the percentages of non-suppression for a series of psychiatric disorders and multiple threshold values of the DST are shown.

		% DST non-suppression			
Diagnostic group	*N*	≥4 μg/dl	≥5 μg/dl	≥10 μg/dl	≥15μg/dl
"Depressive symptoms" (A)	36	19	14	3	3
Major depression—total	104	72	63	38	14
—without melancholia (B)	62	60	48	21	6
—with melancholia (C)	23	87	78	43	9
—with psychosis (D)	19	95	95	84	47
Schizoaffective	7	43	43	29	0
Mania	6	33	33	33	33
Mixed bipolar	7	100	100	43	14
Organic affective syndrome	6	67	67	33	33

Table 3. Rates of dexamethasone non-suppression in psychiatric inpatients (Evans and Nemeroff 1987).

For different mood disorders a pronounced dependence between the severity and the percentage of non-suppression is observed. For the standard threshold of 5 μg/dl cortisol post-DEX the following picture emerges:

"Depressive symptoms" (neurotic?)	14%
Schizoaffective disorder	43%

Depression without melancholia	48%
Depression with melancholia	78%
Depression with psychosis	95%
Mixed bipolar depression	100%

In a more recent review (Murphy 1991) a similar picture was found. Table 4 shows a compilation of the results.

	No. of subjects	Non-suppressors (%)
Major depression		
All adult	4411	43
Young (< 18 yr)	205	34
Elderly (> 60 yr)	183	64
Familial	265	47
Sporadic	379	38
Bipolar	110	38
Melancholic or endogenous	583	50
Psychotic	150	67
Mixed bipolar (manic–depressive)	41	78
Other psychiatric disorders		
Anxiety disorders (incl. panic and phobias)	74	8
Schizophrenia	260	13
Minor depression (dysthymic disorder or endogenous)	238	23
Acute or typical psychoses	69	34
Dementia	174	41
Mania	137	41
Grief reaction	Not stated	10
Controls		
Normal	1130	7
Normal + non-psychiatric patients	1269	8

Table 4. Rates of DST non-suppressors in various psychiatric populations (Murphy 1991).

Again, patients with psychotic depression or mixed bipolar depression show the highest rates of non-suppressors (Nelson and Davis 1997).

The CORE rating scale of Parker and colleagues is probably the currently best tool for the diagnosis of melancholia. A group of 100 mildly to severely depressed inpatients were assessed with the CORE system and subjected to the DST (Parker and Hadzi-Pavlovic 1996). Figure 3 shows an almost perfect linear relationship between the grouped CORE scores and the percentage of non-suppressors per group.

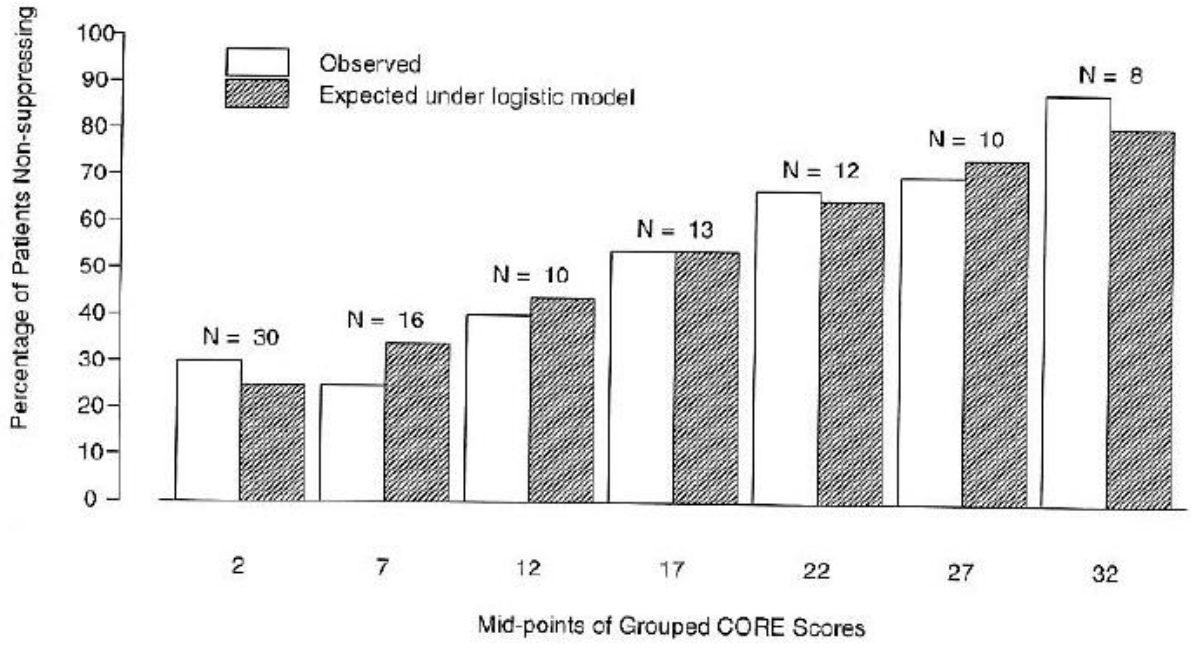

Figure 3. Percentage of observed and expected (logistic regression model) non-suppressors as a function of the CORE score (Parker and Hadzi-Pavlovic 1996).

In the same patient population a similar, although less strong, correlation was found when Newcastle scores were used.

In another study done by Dwight Evans from the University of North Carolina at Chapel Hill the 1 mg overnight DST test was applied to 166 depressed (according to *DSM-III* criteria) inpatients (Evans 1988). Using the 5 µg/dl threshold for the definition of DST non-suppression, he found a marked dependence of the proportions of non-suppressors on the type of depression: "depressive symptoms" (14%), MDD without melancholia (48%), MDD with melancholia (78%) and MDD with psychosis (95%). Interestingly, he also reported a high rate of 17% of subclinical autoimmune thyroiditis in the non-suppressors of the same patient group (vs 3% in the suppressor group).

In 1987 Helmfried Klein, a member of the research group of Hanns Hippius in Munich, published a monograph (probably based on his habilitation thesis) about biological markers in affective disorders in which he comprehensively reviews the published literature about the DST and adds his own research results regarding many aspects of the test in a patient cohort at the university hospital in Munich (Klein 1987).

Klein reviewed the publications regarding the sensitivity and the specificity of the DST in different patient populations. Below his findings (averages) are shown in 2 different ways, based on: i. All studies (irrespective of the parameters of the DST used), ii. Only those studies with DST parameters as proposed by Carroll et al. (i.e., 1 mg DEX p.o., serum cortisol determination at 4 pm post-DEX, threshold >5 µg/dl cortisol).

- Specificity of the DST

a) Healthy controls
In 15 studies (#patients (N)=646) a mean specificity of 93.6% was found. In a subset of 7 studies (N=305) using the DST parameters of Carroll the average specificity was 92.1%.

b) Psychiatric patients (diagnosis other than depression)
In 20 studies (N=656) a mean specificity of 76% was found (i.e., 24% non-suppression). In a subset of 10 studies (N=292) using the DST parameters of Carroll the specificity dropped to 69%.

- Sensitivity of the DST

In a comparison between patients with endogenous and non-endogenous depression, 10 studies with a total of 996 patients were analyzed. In the group of patients with endogenous depression (N=608) the sensitivity was 43%, in the group of patients with non-endogenous depression (N=388) 24%, respectively.

Eighteen studies (N=1,219) with 2 heterogeneous diagnostic groups of depressed patients were analyzed. In the 1st group the following diagnoses of depression were lumped together: primary, endogenous and psychotic. The 2nd groups contained the following diagnoses of depression: secondary, non-psychotic, non-endogenous, minor, bipolar and neurotic/reactive. The proportion of non-suppressors in group 1 is 56%, in group 2 23%, respectively. The overall proportion of non-suppressors in both groups is 40%.
In a subset of 7 studies (N=408) using the DST parameters of Carroll, proportions of non-responders 72% and 42%, were found for group 1 and 2, respectively. Obviously, the diagnoses represented in the groups are very heterogeneous and also the diagnostic criteria highly variable.

- Other relevant results

In a patient cohort at his clinic Klein observed, contrary to the findings of Carroll, a statistically significant difference of the post-DEX dexamethasone concentrations at 4 pm between males and females, which also manifested itself in the corresponding cortisol concentrations (Klein 1987). The results for a dose of 1 mg DEX are shown below.

Gender	DEX (ng/dl)	Cortisol (µg/dl)
Female	62.7	2.25
Male	115.9	0.89

The proportion of non-responders correlated with the severity of the depression, as measured by HAMD.

In 1985 Carroll published another important paper, “Dexamethasone suppression test: a review of contemporary confusion” (Carroll 1985). In the summary we read:

> "Reasons for the current controversy and confusion about the dexamethasone suppression test (DST) are reviewed, and basic axioms regarding use and interpretation of the test are reiterated. Problems with reliability and validity of current diagnostic systems limit their use as 'gold standards' for evaluation the DST; accurate evaluation must await follow-up and treatment response studies. Interpretation of DST results in specific patients requires common sense, consideration of the clinical context, and attention to technical factors. While its ultimate significance is not yet known, the DST, like other laboratory tests, may help to resolve uncertainty in clinical diagnosis. Perhaps most important, it may help to refine current paradigms for psychiatric nosology and diagnosis."

This 12-page article in the *Journal of Clinical Psychiatry* contains many sound arguments concerning the use and interpretation of the DST and also well-reasoned answers concerning contradictory findings of other research groups. The interested reader is encouraged to study this article carefully.

In 1987, the results of a World Health Organization Collaborative Study of the DST were published (WHO 1987). The response to the DST was examined in 543 patients suffering from major depressive illness and 246 healthy controls, from 13 research centers, representing 12 different countries. Some of the results are shown in Table 5.

	Patients		*Controls*	
	Plasma concentration	*% Abnormal response*	*Plasma concentration*	*% Abnormal response*
Basle	82.2 ± 10.9 †	59	—	—
Brussels	93.6 ± 12.3*†	69	13.4 ± 2.4	0
Budapest	65.8 ± 7.2*†	54	21.3 ± 3.3	7
Casablanca	37.4 ± 12.1	25	26.2 ± 8.0	14
Copenhagen	116.5 ± 23.2*†	71	16.5 ± 1.8	0
Epsom	101.0 ± 6.7*†	70	26.2 ± 2.6	11
Irvine	52.6 ± 9.0 †	42	—	—
Lucknow	46.8 ± 8.2 †	48	48.9 ± 9.4	40
Moscow	22.5 ± 4.2	15	—	—
Munich	91.1 ± 10.1*†	62	25.0 ± 3.5	8
Nagasaki	42.0 ± 10.9*	21	13.5 ± 1.0	0
Sapporo	39.3 ± 6.8*	23	16.3 ± 2.0	3
Utrecht	66.8 ± 11.7 †	41	—	—
All centres ($n = 543$)	70.6 ± 2.9 †	($n = 246$)	24.9 ± 1.7	

Table 5. Post-DEX plasma cortisol concentrations (in ng/ml; divide by 10 to get the numbers in µg/dl) and percentages of abnormal DST responses (i.e., non-suppression) of patients and controls (WHO 1987).

Although a substantial variation between the different centers can be observed, the general observation of hypercortisolism and a higher number of positive DSTs in depressed patients is confirmed. The high variation of the cortisol data and the resulting percentages of non-suppressors between centers strongly indicates the need of standardization of all aspects of the DST.

How the DST can be misapplied in the context of depression, is shown in a large cohort study from the Netherlands (Vreeburg, Hoogendijk, van Pelt et al. 2009). A total of 1,588 patients (308 controls, 1,280 patients with MDD) were subjected to the DST and more than 11,000 cortisol determinations (in samples drawn at 7 different time points) were performed.

None of the test parameters, the characteristics of the patient population, nor the definition of depression, as stated by Carroll (Carroll, Feinberg, Greden et al. 1981) were met. The control group showed a higher proportion of non-suppressors (14.9%) than the patients with current MDD (11.0%) and those with remitted MDD (13.8%). The results were judged by the authors to be inconclusive. What else could we have expected?

Features and limitations of the DST

Why was the DST rejected by the psychiatric community more than 30 years ago? As Shorter and Fink (2010), Lutz (2021) and David Healy, Barry Blackwell and Jay Amsterdam (in their 2021 discussions of Lutz's paper on the INHN website) have pointed out, there were a couple of reasons contributing to the fall of the test mostly unrelated to the DST as a scientific procedure. The stated causes are all valid, identifying the impact of the *zeitgeist* and weak points in the personalities of the principal actors, and in the psychiatric community as a whole.

However, as already pointed out by others, the most important criterion for the validity of a scientific test is independent replication. A test must yield similar results in the hands of different researchers. Any test yielding good results only in the lab of a single research group is highly suspicious. Concerning the DST some groups confirmed the findings of Carroll and colleagues, others didn't. No convergence towards the findings of Carroll happened and the dilemma was not resolved. The attempts of the World Health Organization (WHO 1987) and the American Psychiatric Association (APA) (Glassman 1987) to settle this issue through dedicated task forces resulted in the final refusal of the DST.

As Lutz correctly mentions in her paper, the DST was never fully validated and standardized. This is a big shortcoming which calls for trouble of all sorts. We also have to keep in mind that 40 years ago the possibilities of a clinical chemistry laboratory were more limited than they are today. The DST was first introduced in endocrinology for the diagnosis of Cushing's syndrome (Little 1960). Since then, it has become a standard procedure in that field. Unfortunately, it seems that the accumulated knowledge about the test and its performance in endocrinology was not taken into consideration by most psychiatrists.

Let's have a look at some of the scientific issues involved. Many factors unrelated to the DST confound the outcome. They were recognized by Carroll and later amended by other researchers. Liebl and Klein discuss several of these factors (Liebl 1986; Klein 1987).

- The dose and time of application of dexamethasone (DEX)

The doses used for the DST by different research groups were mostly in the range of 0.5 to 2 mg DEX given orally at 11 pm. Carroll chose 1 mg as the best dose, others believed that 2 mg is more appropriate. Hunt and colleagues applied DEX doses of 0.5 and 1.5 mg sequentially to depressed patients and controls and observed significantly different sensitivities of the DST (Hunt, O'Sullivan, Johnson et al. 1991). The optimal dose has never been determined by a sound scientific procedure, nor the best application time. Most likely, the dose and application time are interacting and must be optimized together.

- Quantification of cortisol

Carroll used the competitive protein-binding method (CPB), most other researchers used the more specific radioimmunoassay (RIA). However, different RIAs with different antibodies were used. Richie and colleagues compared the CPB to 16 different commercial RIAs using post-DEX plasma pools (Ritchie, Carroll, Olton et al. 1985). For a cortisol concentration of 5 µg/dl the corresponding concentrations determined by the different RIAs were in the range of 4.3 to 8.7 µg/dl. This finding explains some of the variance in the sensitivity and specificity of the DST found in different studies and calls for a standardization of the analytical procedure and a lab-specific threshold in each laboratory.

Today, more powerful methods for the quantification of cortisol are available. The liquid chromatography-tandem mass spectrometry (LC-MS/MS) method is both highly sensitive and specific (El-Farhan, Rees and Evans 2017). An additional bonus is the capacity to quantify additional important analytes like cortisone and dexamethasone (see below) in the same analytical run.

- Factors influencing the cortisol concentration

One of the most important confounding factors affecting the post-DST cortisol concentration is the DEX blood level at the time of measurement (Meikle 1982; Carr, Morris and Gilliland 1986; Morris, Carr, Gilliland et al. 1986; Maguire, Schweitzer, Biddle et al. 1987). Using a standard dose of DEX, a substantial inter-patient variation has been observed. This has also been recognized by Carrol and colleagues (Ritchie, Belkin, Krishnan et al. 1990; Cassidy, Ritchie, Verghese et al. 2000).

However, to the best of our knowledge, no comprehensive study of the DST incorporating the DEX concentration was ever done. A study from the laboratory of Robert Rubin found that post-DEX serum dexamethasone concentrations significantly influenced DST outcome only when they were below a certain threshold level (Poland, Rubin, Lesser et al. 1987). Too low DEX concentrations resulted in a substantial proportion of false-positive DSTs. Low DEX levels have been attributed to a polymorphism of the metabolizing enzyme cytochrome CYP3A4 causing rapid metabolism, or to the use of drugs that induce the production of this enzyme. Other potential causes include low gastrointestinal absorption and increased distribution of DEX due to low albumin binding.

The elimination of DEX could also be affected by reduced liver and kidney functions (Ueland, Methlie, Kellmann, et al. 2017). Impaired DEX metabolism and other factors can also result in too high concentrations, which might cause false-negative DST results. This large inter-patient variation of dexamethasone was one of the most important scientific reasons for the final rejection of the DST.

As only the free cortisol (and also free dexamethasone) is biologically active, the concentration of corticosteroid binding globulin (CBG, and other binding proteins) is also of importance and must be taken into consideration (Yener, Tuna, Kant et al. 2021). Concentrations of free cortisol (and dexamethasone) could be obtained directly by using saliva instead of blood (Zhang, Dou, Gu et al. 2013). The sampling of saliva would make the whole procedure simpler and allow easily for multiple samples. The DEX concentration should be determined at the same time as the cortisol to make sure that the test results are reliable. Lower or higher DEX concentrations might result in false-positive or false-negative results of non-suppression, respectively.

- The decision criterion

The criterion for the classification of the outcome of the DST (i.e., non-suppression vs suppression) as proposed by Carroll is simply the cortisol threshold (cut-off) of 5 µg/dl (which has to be individually determined for each laboratory). Other criteria, like the difference or the quotient of basal (pre-DEX) and post-DEX cortisol have been proposed, yielding only little, if any improvement.

Obviously, beside the post-DEX cortisol concentration, multiple other factors (e.g., DEX concentration, basal cortisol levels, cortisol metabolite levels and patient demographics (age, gender, etc.)) might have an important impact on the outcome of the DST. These factors should be included in the building of a predictive model with optimal performance (Mitchell, Hadzi-Pavlovic, Parker et al. 1996; Mossman and Somoza 1989). Another important aspect is the continuous nature of the cortisol concentration. Any binarization will reduce the information content. It is much better to use the numerical outcome, instead of a binary response (e.g., ≤ 5 vs > 5 µg/dl). Small deviations of post-DEX cortisol measurements close to the threshold value influence the outcome label, but it is evident that a reading of 4.99 (suppression) is not significantly different from 5.01 (non-suppression). Even the use of confidence intervals, the repetition of measurements close to the threshold or the use of averages does not eliminate this conceptual problem. Instead of the simple decision criterion proposed by Carroll, an advanced model which yields a case-wise probability of being a non-suppressor would be advantageous (Carroll 2013, 2017).

- The secretion pattern of cortisol

The 24-h circadian secretion rhythm of cortisol is well known (Sachar 1976c). However, that there is an additional superimposed ultradian rhythm, is less known. Figures 4 to 7 show real examples of these two rhythms based on high-frequency cortisol measurements in healthy controls, depressed patients and patients with hypercortisolism (Cushing's disease/syndrome).

The cortisol profiles indicate that there is a large inter-individual variance of the cortisol levels at a given time. Cortisol is secreted in pulses of a rather high amplitude. Linkowski and colleagues report absolute cortisol pulse amplitudes of 6.8, 6.3 and 7.8 µg/dl for normal controls, unipolar and bipolar depressed patients, respectively (Linkowski, Mendlewicz, Leclercq et al. 1985). This is also true for the afternoon post-DEX period, when the most important cortisol measurements are made. This observation can have a huge impact on the outcome of the DST, as the timing of the pulses is variable and the difference between cortisol concentrations at the peak of a pulse and the baseline can be substantial.

Mark Gold and colleagues did a DST study including 65 patients with "primary major depression" in which cortisol was quantified at 6 different times between 8 am and 12 pm post-DEX. They found that when applying the standard procedure of Carroll (2 measurements post-DEX at 4 and 11-12 pm) 31% of the patients were found to be non-suppressors. When all 6 cortisol measurements were used (i.e., cortisol conc. at any time point > 5µg/dl) the proportion of non-suppressors rose to 44% (Extein, Pottash and Gold 1985; Goggans, Wilson Jr, Gold et al. 1983). Using the average or maximum of multiple measurements done during a period of several hours in the afternoon post-DEX can solve this problem.

Figure 4 shows a representative cortisol profile in a healthy young man. In Figure 5 cortisol profiles of one healthy person and 3 patients with different types of Cushing's syndrome are represented. In all patient profiles the hypercortisolemia and the pulsatile secretion of cortisol is clearly visible.

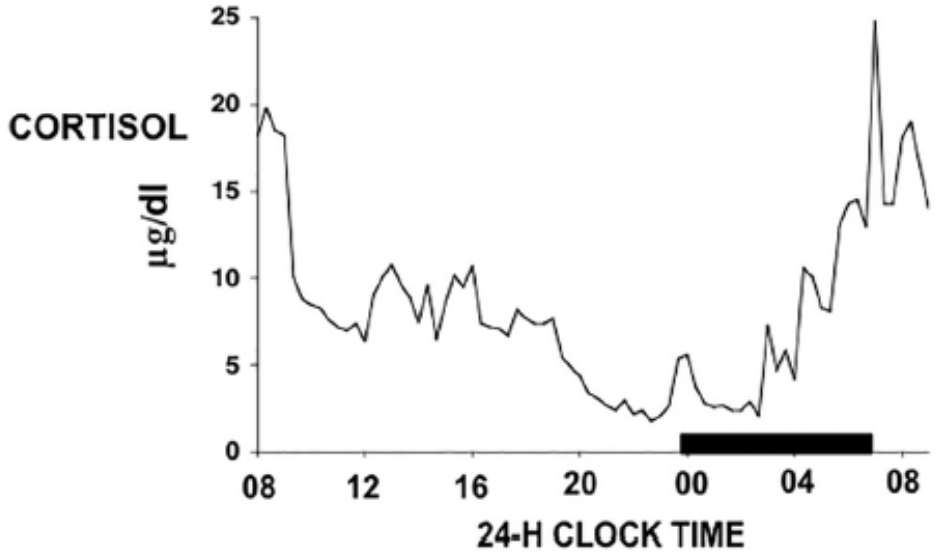

Figure 4. Representative 24-hour profile of plasma cortisol levels sampled at 15-minute intervals in a healthy young man studied under normal conditions (Sleep time shown as a black bar) (Oster, Challet, Ott et al. 2017).

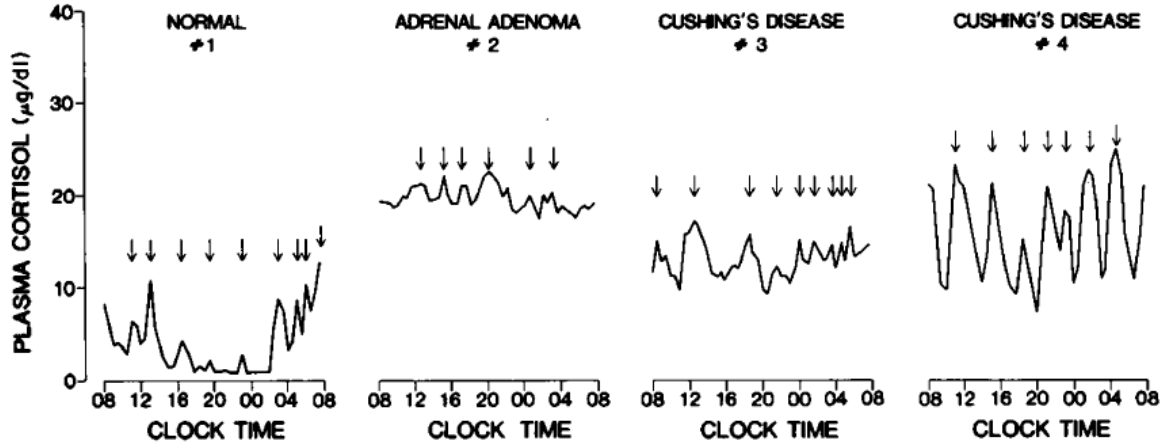

Figure 5. 24-hour profiles of plasma cortisol levels measured at 30-min intervals in one normal volunteer (#1), one patient with adrenal adenoma (#2, Cushing's syndrome) and two patients with Cushing's disease (#3 and #4). Significant episodic spikes are indicated by arrows (Van Cauter and Refetoff 1985).

In Figure 6 high-resolution cortisol profiles of 2 healthy volunteers are shown. As can be seen, the number, temporal position, as well as the amplitude of the cortisol pulses show a large inter-individual variation.

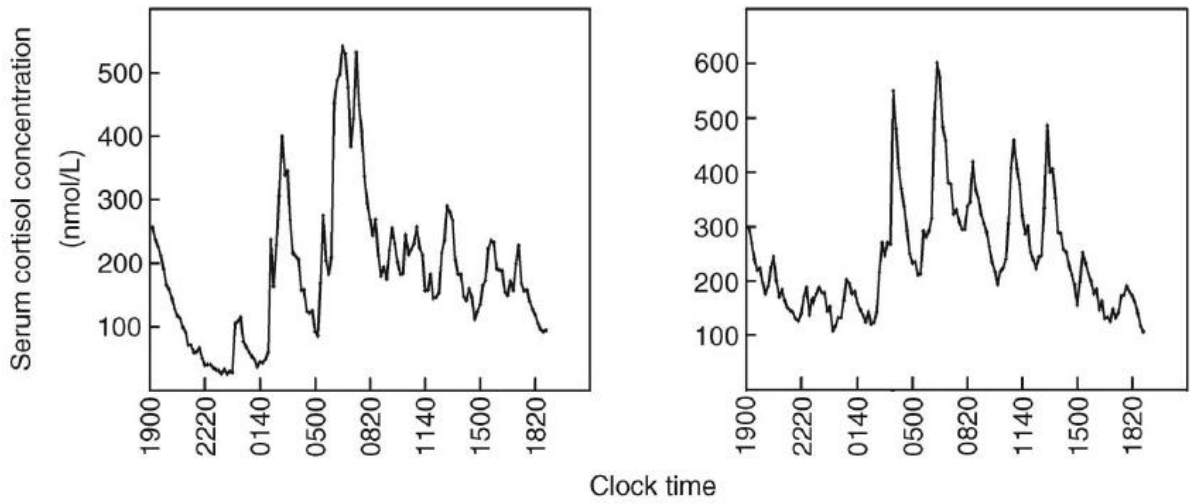

Figure 6. Profiles of serum cortisol concentrations of two healthy male volunteers. Rapid (10-minute) automated sampling reveals the circadian profile and the underlying ultradian rhythm (to get concentrations in µg/dl multiply cortisol values by 0.03625) (Henley, Leendertz, Russell et al. 2009).

The cortisol profile on the left of Figure 7 shows that the pulsatile secretion of cortisol is maintained in a depressed subject.

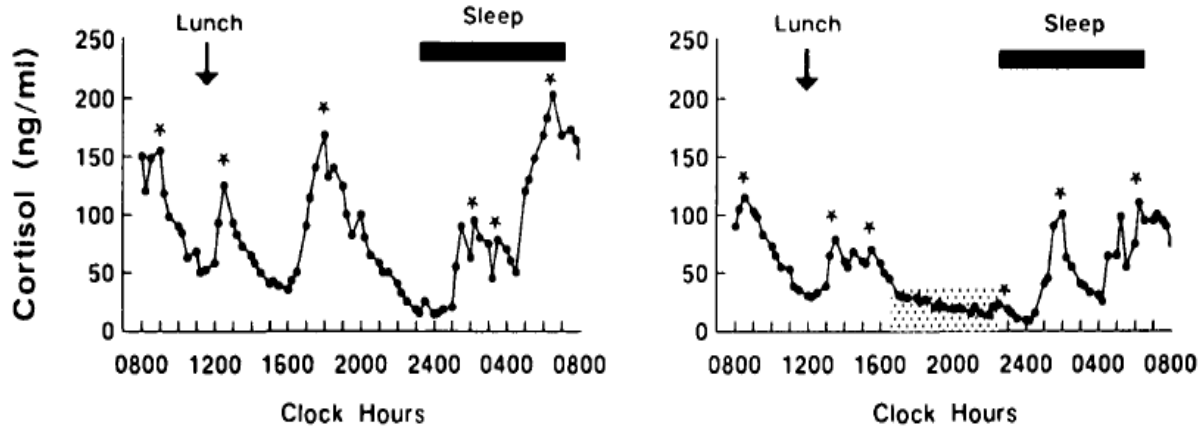

Figure 7. The circadian and pulsatile serum cortisol secretory patterns in a depressed (left) and a normal (right) woman. The stars indicate significant cortisol pulses (Mortola, Liu, Gillin et al. 1987).

More recently, Carroll and colleagues published an in-depth study of the pulsatile secretion of cortisol and ACTH in depressed patients using high-frequency blood sampling (Carroll, Cassidy, Naftolowitz et al. 2007). Depressed patients with and without hypercortisolism were clearly distinguished. In hypercortisolemic depression (i.e., severe depression with hypercortisolism), cortisol secretion is irregular and is uncoupled from ACTH

secretion.

Nosological aspects

Carroll, in his 1981 publication "A specific laboratory test for the diagnosis of melancholia" proposed the DST as a tool for the diagnosis of melancholia. Obviously, the definition of melancholia and the reliability of this diagnosis is of great importance for the performance of the DST (i.e., its sensitivity and specificity).

What is melancholia? This question might be considered to be a naïve, but nevertheless it is very relevant because there is still no consensus in the psychiatric community about melancholia as a mental disease *sui generis*, nor the characteristics uniquely describing it. Melancholia (qua endogenous, endogenomorphic or vital depression) has been described as a clinical entity for millennia and was well accepted by the alienists of the past.

However, even Emil Kraepelin made melancholia part of *manic-depressive insanity* (MDI) only in the 8th (the last edition) of his textbook, which was published in 4 volumes in the years 1909-1915. Before this, he considered melancholia to be part of a separate group of involutional disorders (Kendler and Engstrom 2020). This is what Kraepelin wrote about melancholia:

> "Melancholia and raving madness (*Tollheit*) are well-known forms of insanity. Melancholia is the term used for sad or anxious moods, which are usually accompanied by delusions in the sense of sin (*Versündigung*) or persecution... The majority of the cases so characterized is, as we know today, manic-depressive insanity; another part belongs to dementia praecox, still other cases to paralysis, sporadically also to epilepsy, to arteriosclerosis, to degenerative insanity. Since also certain depressive states of the involutional years, which I believed to be independent, are probably to be classified among the diseases known to us, as far as a clinical understanding is possible at all today, melancholia has lost its justification as a form of disease and will have to be regarded only as a condition" (Kraepelin 1909).

With the advent of *DSM-III* in 1980, melancholia was lumped together with other depressions of the neurotic/reactive type under the label *major depressive disorder* (MDD). This resulted in a very heterogeneous entity with ever since has hindered the progress in depression research and psychopharmacology and is lamented by many experts (Amerio, Odone, Marchesi et al. 2014; Ghaemi and Vöhringer 2011; Shorter 2007). More recently, several experts have called for a reinstitution of melancholia as a valid disease entity (Fink, Bolwig, Parker et al. 2007; Parker, Fink, Shorter et al. 2010). The subject of melancholia is also described in a comprehensive way in several books (Parker and Hadzi-Pavlovic 1996; Taylor and Fink 2006). The currently most reliable diagnostic tool for melancholia is probably the CORE measure (Parker and Hadzi-Pavlovic 1996; Parker, Fink, Shorter et al. 2010). Following this definition of melancholia, psychotic depression, bipolar depression, mixed bipolar depression and probably also schizoaffective psychosis are all part of it.

Now we come to the important topic of the diagnostic systems Carroll and other researchers who investigated the performance of the DST used. Carroll and colleagues made use of a *clinical diagnosis* of melancholia which is fully described in the article "The Diagnosis

of Endogenous Depression in the Journal of Affective Disorders" (Carroll, Feinberg, Greden et al. 1980). In addition to the application of a structured psychiatric interview, the Schedule for Affective Disorders and Schizophrenia (SADS), the patient's previous psychiatric history, family history and past hospital records were taken into consideration. The major diagnostic features of endogenous depression (i.e., melancholia) were: i. History of mania, hypomania or endogenous depression, ii. Definite family history, iii. Severe agitation or retardation, iv. Depressive psychosis, v. Pervasive anhedonia, vi. Definite pathological guilt. The severity of the depression was quantified by the Hamilton rating scale and by the Carroll self-rating scale (Carroll, Feinberg, Greden et al.1980).

Other researchers mostly used only symptom-based tools like the *RDC* or the *DSM-III*. In some investigations the more appropriate Newcastle scale (Carney, Roth and Garside 1965; Zimmerman, Coryell and Pfohl 1986a; Zimmerman, Pfohl, Stangl et al. 1986b) was used. It must be clearly stated that the vast majority of other researchers investigating the DST did not use the Carroll-Feinberg definition and diagnostic criteria of melancholia. Instead, broader (and less appropriate) definitions of melancholia were applied, explaining partially the inconsistent results across studies.

Mark Zimmerman and colleagues from the University of Iowa examined the relationship between the performance of the DST and 4 definitions of endogenous depression, namely *DSM-III*, Feinberg and Carroll, Newcastle and *RDC* (Zimmerman, Coryell, Pfohl and Stangl 1985). They found rather similar percentages (36-48%) of non-suppressors in groups of patients with the diagnosis of "definite endogenous depression."

One has to keep in mind that *per se* none of the tools used for the diagnosis of melancholia is correct, because there is no valid gold standard. Hui and Zhou from the Division of Biostatistics at the Indiana University School of Medicine reviewed statistical methods developed to estimate the sensitivity and specificity of screening or diagnostic tests when the fallible tests are not evaluated against a gold standard (Hui and Zhou 1998).

Medical causes of mental disorders

Perhaps one of the most important, but certainly the darkest area of psychiatric etiology (Ursachenlehre) is that of metabolic diseases.
Emil Kraepelin (Kraepelin 1909)

In 1980, the American Psychiatric Association restated the need for careful medical evaluation of psychiatric patients by incorporating physical disorders as one of three diagnostic axes. In its third edition of the Diagnostic and Statistical Manual (DSM-III), the diagnostic criteria further require the exclusion of physical causes of mental symptoms: the clinician must determine that the diagnoses of Axis I are "not due to an organic mental disorder." The impact of these changes is profound: the psychiatrist must consider the effects that an underlying medical disorder may have in producing specific psychiatric symptoms, and he or she must examine and further evaluate patients to rule out such disorders.
Richard C. W. Hall (Hall, Beresford, Blow et al. 1990)

Symptoms of aberrant behavior, mood, perception, and thinking modalities are observed not only within the domain of psychiatry proper. They regularly accompany the widest varieties of

physical illness and toxic states as well. In many instances such symptoms can represent the first manifestation of a physical illness and can precede other signs or clinical display by years. Thus, such symptoms can be entirely unspecific in nature… In fact, no psychiatric symptoms exist that at times cannot be caused or aggravated by a variety of medical illnesses. Erwin K. Koranyi and Walter M. Potoczny (Koranyi and Potoczny 1998)

The association between physical illnesses and mental symptoms has been recognized for a long time. There are in particular two physical illnesses which contributed to the establishment of biological psychiatry: i. Pellagra, a vitamin deficiency, and ii. Syphilis, a bacterial infection. Both can have a profound effect on the brain and mental functioning. Delirium, dementia, psychosis and depression were common neuropsychiatric features of pellagra (vitamin B3/niacin deficiency) as seen in the 18th and 19th centuries in Europe and in the early part of the 20th century in the United States (Lanska 2010). Syphilis, an infectious disease caused by the spirochete *treponema pallidum,* is known in medicine as the "great imitator." It can cause a multitude of different clinical pictures, including those of (almost) all mental disorders. When only mental symptoms are present and no targeted serological tests are ordered, the correct diagnosis can easily be missed. When the brain is affected, this disease is called *General Paralysis of the Insane* (GPI). Before the availability of antibiotics starting in the 1940s, a substantial proportion of inmates in mental institutions suffered from GPI. Today, neurosyphilis is less common but still a real possibility with rising incidences in many countries and should not be overlooked by the practicing psychiatrist. Another spirochete, *borrelia burgdorferi,* known to be the infectious agent of *Lyme disease,* is also a great imitator and can cause many neuropsychiatric symptoms. Its diagnosis and treatment are sometimes difficult, if missed in the early phase of the infection.

The association between endocrine disorders and mental symptoms was recognized a long time ago. Among them are *myxedema* (hypothyroidism), *Addison's disease* (hypocortisolism), *Graves' disease* (hyperthyroidism) and *Cushing's disease* (hypercortisolism). The connection between endocrine diseases and affective disorders has been studied intensively by Giovanni Fava and coworkers and resulted in a substantial number of publications (e.g., Fava, Sonino and Morphy 1987; Fava 1994b).

In 1978, at a time when neurology had little to say about the mind, while psychiatry was strongly influenced by psychoanalysis, British neuropsychiatrist William Alwyn Lishman published the first edition of his influential textbook *Organic Psychiatry* (Lishman 1997; David, Fleminger, Kopelman et al. 2009), describing many neurological and somatic causes of mental symptoms. Another excellent resource is David Moore's *Textbook of Clinical Neuropsychiatry and Behavioral Neuroscience* (Moore and Puri 2012). For those interested in the state of the art in the 1950s, the information-packed book of McCarthy and Corrin (1955) is recommended. In these books many different somatic diseases and their association with mental symptoms are discussed. Below is a partial list:

- Nutritional deficiencies (vitamins, minerals, trace elements)
- Neoplasms/tumors
- Epilepsy
- Autoimmune diseases
- Infections (viral, bacterial, protozoal, etc.)
- Brain injuries

- Metabolic disorders
- Cerebrovascular disorders
- Cardiovascular disorders
- Electrolyte disorders
- Intoxications (heavy metals, organic chemicals)
- Neurodegenerative disorders
- Medications and drugs

Many physical diseases and pathological conditions are potentially associated with mental disturbances. These relationships are well documented in the literature, but often unknown or neglected by clinical psychiatrists. Many contemporary psychiatry textbooks contain only little or no in-depth information about secondary mental disorders and their causes. One laudable exception is the textbook by Columbia University psychiatry professors Janis Cutler and Eric Markus (2010). The, by psychiatrists, probably most well-known relevant physical disease as a cause of depression is hypothyroidism. But even this disease might be missed due to an undue reliance on lab data for the thyroid-stimulating hormone (TSH), a too broad TSH normal range, unknown concentrations of free T3/T4 and/or thyroid-specific autoantibodies.

What about the numbers? How important are these somatic diseases for psychiatry? Several investigators have determined the prevalences or incidences of physical diseases in psychiatric patient cohorts in different settings. Canadian psychiatrists Erwin Koranyi and Walter Potoczny published a comprehensive review of 21 such studies comprising a total of 9,199 psychiatric patients (Koranyi and Potoczny 1998, see also: Koranyi and Potoczny 1992). The results of these studies are shown in Table 6.

Authors	Year	Number of patients	Rate of physical illnesses, %	Direct relation to psycho-pathology, %	Priorly un-diagnosed %
Phillips [24]	1937	164	45	24	?
Marshall [26]	1949	?	44	?	?
Herrige [27]	1960	209	50	?	?
Davies [28]	1965	36	58	42	?
Maguire and Granville-Grossman [29]	1968	200	33	?	49
Johnson [30]	1968	250	60	12	80
Koranyi [25]	1972	100	49	20	71
Burke [31]	1972	202	43	?	?
Eastwood [32]	1975	124	? 'high'	?	?
Etamad [33]	1978	3,542	50	?	?
Burke [34]	1978	133	50	?	?
Hall et al. [35]	1978	658	?	9	46
Koranyi [1]	1979	2,090	43	18	46
Buckley et al. [36]	1980	200	52	?	?
Hall et al. [37]	1980	100	80	46	46
Ferguson and Dudleston [38]	1986	650	17	?	?
Marcil et al. [39]	1987	50	56	?	?
Pary and Barton [40]	1988	110	54	?	?
Honig et al. [41]	1989	218	80	46	46
Knutsen and DuRand [42]	1991	78	56	?	56
Mahendru et al. [43]	1991	85	32	?	84
Total		9,199	50.10	27.12	58.22

Table 6. Comparative results of physical illnesses in psychiatric patients (Koranyi and Potoczny 1998).

The average rate of physical illnesses found in those patients is an astonishingly 50%. In 27% of the patients, their illness was judged to be in direct relation to their psychopathology. It is also interesting to learn that 58% of the illnesses detected in these studies were undiagnosed before admission. We have to keep in mind that most of these patients will have undergone a "routine" physical examination or even a more thorough examination by the referring physician. Koranyi and Potoczny close their paper with these words: "the need for careful medical scrutiny of all psychiatric patients can only be strongly emphasized along with the fact that the evaluation of psychiatric patients is a medical responsibility."

One of the studies listed in Table 5 was performed by Koranyi himself (Koranyi 1979) and additional interesting details were published. Over a period of 7 years, all psychiatric patients admitted at the Ottawa General Hospital were at entrance subjected to a comprehensive psychological and physical examination, including a laboratory screening. If indicated, further testing was initiated. Of the 2,090 patients, 43% suffered from a major physical illness. Of those 902 medically ill patients, 46% were undiagnosed by the referring physicians and their physical pathological conditions were only discovered at the psychiatric clinic. The identified physical illnesses showed a strong relatedness to the presenting psychiatric symptomatology.

In 18% of the medically ill patients the somatic pathological condition was judged causative, in 51% as substantially aggravating and in 31% as coexisting with the psychiatric condition. Relative to the total number of admitted patients, the proportions of those with a somatic illness causing or severely aggravating the psychiatric symptoms were 8% and 22%, respectively. These are numbers which cannot be dismissed easily. In the 902 patients with physical diseases, a total of 1,298 disease instances (i.e., 1.44 diseases/patient) were identified. Table 7 shows a compilation of the diseases and their frequencies.

Diseases	Diagnosed on Psychiatry	Known on Referral	Total
Infective and parasitic including instances of infectious hepatitis, syphilis (all types), lymphogranuloma venereum, condyloma acuminata, malaria, *Ancylostoma duodenale,* infectious mononucleosis, extrahepatic amebiasis, and others	26	15	41
Neoplasms including instances of bronchogenic carcinoma, cancer of stomach, pancreas, cervix, breast, malignant and nonmalignant tumors of brain and others	13	29	42
Endocrine, nutritional, and metabolic including instances of diabetes mellitus, hypoglycemia, thyrotoxicosis (all types), myxedema, Hashimoto's disease, Klinefelter's syndrome, alcoholic and nutritional vitamin deficiencies, and others	127	34	161
Blood and blood forming organs including macrocytic and microcytic anemias, hemoglobinopathies, favism, thalassemia minor, polycythemia vera, lymphatic leukemia, and others	47	8	55
CNS excluding neoplasms, except Recklinghausen's disease; includes instances of epilepsy (all types), temporal lobe epilepsy, postencephalitic states, encephalopathies, demyelinating diseases, hereditary disorders, and others	129	121	250
Circulatory system including coronary heart disease (all forms), hypertensive heart disease, chronic rheumatic heart disease, cerebrovascular disease, and others	193	231	424
Respiratory system including instances of asthma, chronic obstructive lung disease (excluding neoplasms), and others	27	49	76
Digestive system including instances of gastric and duodenal ulcer, symptomatic hiatus hernia, symptomatic postgastrectomy state, colitis, cirrhosis of liver, pancreatitis (excluding malignancies), and others	53	61	114
Genitourinary system including acute and chronic nephritis, infective diseases of prostate, ulcer of cervix, endometriosis (excluding malignant neoplasms), and others	16	41	57
Skin and subcutaneous tissue excluding acute and chronic dermatitis, psoriasis; including erythema multiforme, pityriasis, and others	12	22	34
Musculoskeletal system and connective tissues including instances of systemic lupus erythematosus	1	3	4
Adverse drug reactions	37	3	40
Total	**681**	**617**	**1,298**

Table 7. Number and types of medical diagnoses in 902 psychiatric patients with physical illnesses (Koranyi 1979).

We believe that with the capabilities of a modern clinical chemistry/microbiology laboratory (e.g., the detection of neural autoantibodies) and advanced imaging techniques (CT, MRT and positron emission tomography [PET]), when compared with those more than 40 years ago, the number of identified somatic diseases would be even greater.

Almost any physical disease can provoke mental symptoms via the causation of an encephalopathy. Such an encephalopathy can be soft without any neurological signs. It is important to understand that the concomitant psychiatric symptoms are not disease specific. There are many possible physical causes (e.g., neurological diseases, head trauma, infections, autoimmune diseases, vitamin deficiencies, intoxications). Even entirely different diseases, like hypocortisolism (Addison's disease) and hypercortisolism (Cushing's disease), can cause the same clinical picture, namely depression.

There are a number of excellent resources providing a comprehensive overview of physical conditions associated with mental symptoms (Jefferson and Marshall 1981; Extein and Gold 1986; Schiffer, Klein and Sider 1988; Assad 1995; Schildkrout 2011, 2014; Cardinal and Bullmore 2011; Morrison 2015; Skaer 2018). The book *A Dose of Sanity* by psychiatrist and neurologist Sydney Walker III contains a series of interesting case vignettes, showing how easily a somatic condition in psychiatric patients can be missed (Walker 1996).

The human brain is a very sensitive organ which reacts easily to any pathological condition or the disruption of its homeostasis, even before other organs do. Obviously, the brain has only a limited number of ways to express a dysfunction (e.g., delirium, psychosis, anxiety, depression, mania, emotional instability). These are usually summed-up under the term *organic brain syndrome* (also called o*rganic psychosyndrome*). The commonly reported psychological symptoms include loss of memory and concentration, emotional liability, fatigue, depression, severe anxiety and reduced intellectual ability. The early identification of this syndrome in the context of psychiatric symptoms is very important (Taylor 2007). Especially in older people, new-onset psychiatric symptoms often have a somatic cause.

Because of the sensitivity of the brain, mental symptoms occur often when the physical disease is not (yet) manifest. In prodromal states and subclinical diseases, the correct diagnosis of the underlying cause of a mental disorder calls for a high level of suspicion and an in-depth investigation (Fava, Morphy and Sonino 1994a; Fava 1999). This explains why many organic causes are not detected. In Table 8 some medical diseases with affective prodromes are shown.

	Depression	Anxiety	Irritability
Endocrine diseases	Cushing's syndrome Addison's disease hyperthyroidism hypothyroidism hyperparathyroidism hyperprolactinemia	Cushing's syndrome hyperthyroidism hypothyroidism hyperparathyroidism pheochromocytoma	Cushing's syndrome Addison's disease hyperthyroidism hyperparathyroidism hyperprolactinemia
Neurological diseases	cerebral tumors Parkinson's disease Huntington's disease multiple sclerosis normal pressure hydrocephalus Alzheimer's disease	cerebral tumors Huntington's disease multiple sclerosis Wilson's disease temporal lobe epilepsy cerebral insufficiency	cerebral tumors temporal lobe epilepsy Alzheimer's disease
Other diseases	carcinoma of pancreas lung cancer lymphomas hepatitis encephalitis AIDS	recurrent pulmonary emboli	

Table 8. Affective illnesses with prodromal affective symptoms (Fava, Morphy and Sonino 1994a).

In their review, Cosci and colleagues analyzed a total of 21 studies, assessing the early manifestations of medical disease as mood or anxiety disorders (Cosci, Fava and Sonino 2015). Depression was found to be the most common affective prodrome of medical disorders and was consistently reported in Cushing's syndrome, hypothyroidism, hyperparathyroidism, pancreatic and lung cancer, myocardial infarction, Wilson's disease and AIDS. Mania, anxiety and irritability were less frequent. Their results are shown in Table 9.

Medical illness	Clinical characteristics
Endocrine diseases	
Cushing's syndrome	Major depression, often melancholic subtype; common symptoms: irritability and emotional lability, change in appetite or weight, loss of energy, change in sleep, anhedonia, psychomotor retardation or agitation, decreased concentration, suicidal thoughts [11–13]
Hypothyroidism	Depression, anergia [14, 15]
Primary hyperparathyroidism	Depression, tiredness, forgetfulness, decreased concentration, uneasiness, sleeplessness [16] Irritability [16]
Neurological diseases	
Multiple sclerosis	Major depressive disorder, dysthymia [17]
Meningiomas	Major depressive disorder and/or anxiety [18]
Parkinson's disease	Major depression and anxiety [19–21]
Malignancies	
Pancreatic cancer	Depression described as 'loss of ambition', 'loss of push' or 'lack of go', anxiety, insomnia, decreased appetite and weight loss, premonition or foreboding of having cancer [23–26] Restlessness, agitation, anxiety [24] Irritability [24]
Lung cancer	Depression [27, 28] Anxiety [28]
Gastric cancer	Irritability [24]
Miscellaneous	
Myocardial infarction	Major depressive disorder, demoralization [30, 31] Somatic anxiety, generalized anxiety, panic, agoraphobia [31] Irritability [31]
Wilson's disease	Depression [29] Mania: increased talkativeness, restlessness, marked mood changes [29] Anxiety [29] Irritability and aggression [29]
AIDS	Somatic and nonsomatic symptoms of depression (sadness, anhedonia, low mood) [34]

Table 9. Early manifestations of medical disease as mood or anxiety disorders (Cosci, Fava and Sonino 2015).

Now we will focus our attention to endocrine disorders and their association with mental symptoms, in particular mood disorders.

The central element of the endocrine system is the pituitary (hypophysis). It is situated right below the hypothalamus in an osseous cavity and is not considered to be a part of the brain. Figure 9 shows a sketch of the hypothalamus-pituitary axis, the different target endocrine glands regulated by it, as well as the different hormones secreted by the pituitary. Another two endocrine glands, the pancreas and the pineal gland (epiphysis), are not shown. The pancreas secretes the hormones insulin and glucagon, the pineal gland secretes melatonin. Endocrine glands are ductless glands of the endocrine system that secrete their products, hormones, directly into the blood. Only the hypothalamus and the pineal gland are part of the brain and are called neuroendocrine organs.

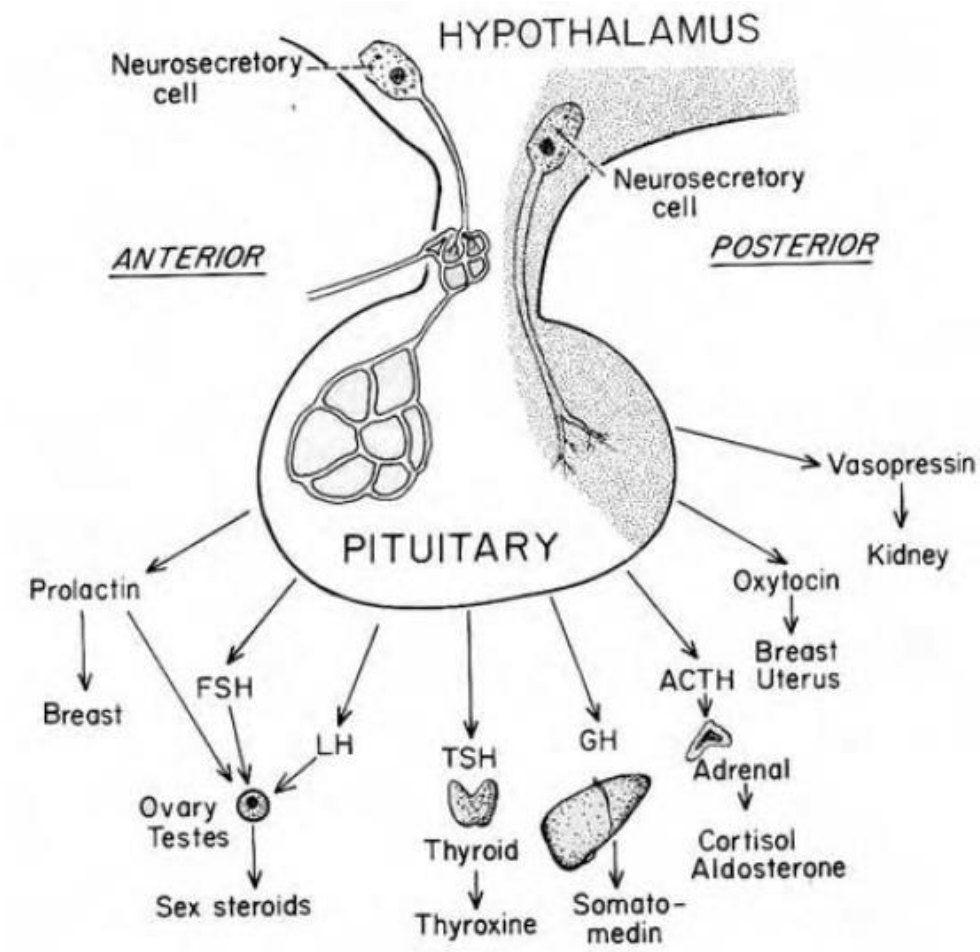

Figure 8. The centrality of the hypothalamus-pituitary axis and the different hormones secreted by the pituitary (Pfaff, Phillips and Rubin 2004).

The relationship between the endocrine system and the brain has been well described by neurobiologist Donald Pfaff: “The brain has been referred to by some as the “largest gland in the body. While this may be hyperbole, it serves to highlight the close functional relationships between the brain and endocrine systems. The pituitary, the so-called master gland, is closely regulated by the brain, being anatomically connected to the hypothalamic area by the pituitary stalk. The hypothalamus is a major integrating center for many other areas of the brain and, through specialized secretions, provides the primary functional regulation of the anterior and posterior pituitary gland. The hormones secreted by the pituitary, in turn, regulate the output of other endocrine glands throughout the body, as well as having direct metabolic effects themselves. Most of the hormones secreted by the hypothalamus, the anterior and posterior pituitary, and the peripheral endocrine glands in turn can profoundly affect brain function. Thus, there is a full reciprocity in the concept of hormone–behavior relations” (Pfaff, Rubin, Schneider et al. 2018).

As Pfaff clearly states, almost all hormones can alter brain function and therefore be the cause of psychiatric symptoms. In psychiatry, the two most well-known parts of the endocrine system are the HPA- and the HPT (hypothalamus-pituitary-thyroid)-axes. The others are also important and should not be neglected. For example, diabetes and carcinoma of the pancreas (already in its prodromal state), are strongly associated with depression. Figure 9 shows the prevalence of depression found in patients with 6 selected endocrine disorders.

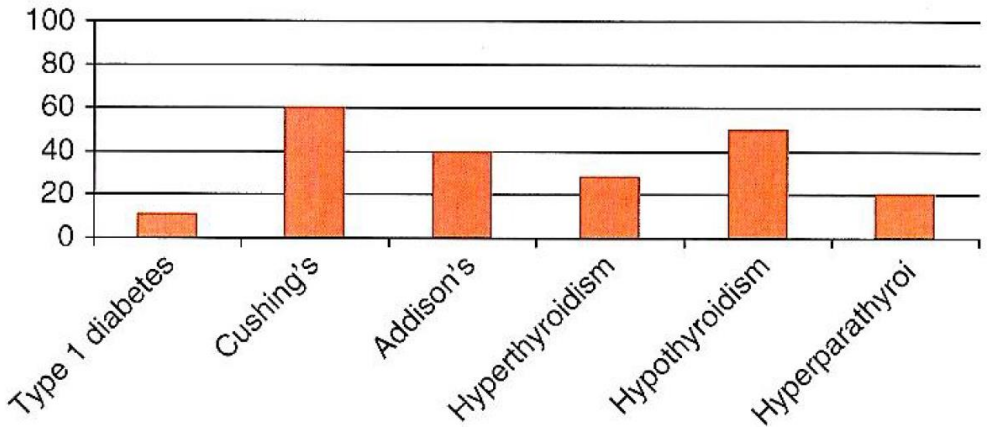

Figure 9. Mean prevalences of depression for selected endocrine disorders (Barsky and Silbersweig 2017).

Two diseases linked to a dysfunctional HPA-axis, Cushing’s and Addison’s disease, are among those with the highest prevalences of depression. Those with a dysfunction of the HPT-axis, hypo- and hyperthyroidism, have only slightly smaller prevalences.

Richard Hall provides a list of medical illnesses which often cause severe depression (Table 10). Out of the 26 listed diseases, 8 (31%) are endocrine diseases.

Pernicious anemia
Folic acid deficiency
Multiple sclerosis
Influenza
Viral hepatitis
Cirrhosis
Uremia
Disseminate carcinomatosis
Oat-Cell carcinoma of the lung
Lymphomas
Chronic myelogenous leukemia
Carcinoma of the pancreas
Cushing's disease
Hyperaldosteronism
Addison's disease
Hyperparathyroidism
Hypoparathyroidism
Hyperthyroidism
Hypothyroidism
Acromegaly
Systemic lupus erythematosus
Ulcerative colitis
Regional enteritis
Whipple's disease
Amyloidosis

Table 10. Medical illnesses that frequently induce depression (Hall 1980).

Depression and anxiety states are the psychiatric reactions most likely to be associated with a concurrent physical disease, or to be caused by a yet undetected medical disease. There is a plethora of possible organic conditions associated with depression. Illnesses as different as a carcinoma and an electrolyte imbalance can give rise to similar psychiatric symptoms. American psychiatrist Richard Hall provides a list of 75 medical conditions presenting with depression (Hall 1980). Giannini and colleagues in their handbook list more than 90 somatic causes of depression (Giannini, Black and Goettsche 1978; Morrison 2015; Whitlock 1982; Robertson 1997; Cardinal and Bullmore 2011; Gold and Pottash 1986; Hall and Beresford 1984).

In his publication *Neuroendocrine Probes as Biological Markers of Affective Disorders,* Canadian psychiatrist Gregory Brown reviews five endocrine systems: the hypothalamic-pituitary-adrenal axis, hypothalamic-pituitary-thyroid axis, growth hormone regulation, prolactin regulation and pineal function (Brown 1989). Abnormalities in all these systems have been found in depressed patients.

There are a few studies in which multiple endocrine axes in the same cohort of depressed patients were assessed. Extein, Pottash and Gold applied both the thyrotropin-releasing hormone (TRH) test and the DST (1 mg DEX, cortisol measurements at 8am, noon, 4pm and midnight post-DEX, threshold: $\geq$ 6 µg cortisol/dl) to a cohort of 50 inpatients with unipolar depression according to RDC criteria. All patients were euthyroid and without evidence of endocrine disease. A total of 84% of the patients showed a dysfunction of the HPA or HPT axis, 34% of the HPT axis only, 20% of the HPA only, and 30% of both axes,

respectively. 64% had a blunted TSH response to TRH, and 50% failed to suppress on the DST (Extein, Pottash and Gold 1981).

Gordon Parker and colleagues assessed the function of three different endocrine axes in 40 inpatients meeting *DSM-III-R* criteria for MDD with melancholia (19 with and 21 without psychosis, respectively). Eighty per cent of the patients showed disturbances in at least one hormonal axis, 40% in 2 axes and 5% in all 3 axes. Growth hormone (GH) blunting was found in 62.5% of patients, DST non-suppression in 37.5% and TSH blunting in 25.0% (Contreras, Menchon, Urretavizcaya et al. 2007).

Many organic illnesses have a recurrent or intermittent course. Organic illnesses can also cause recurrent mental symptoms, suggesting a "psychogenic" disorder and making the detection of the underlying disease more difficult. Gustave Newman lists the following diseases: multiple sclerosis, acute intermittent porphyria, pheochromocytoma, systemic lupus erythematosis, pancreatitis, herpes simplex encephalitis and episodic dyscontrol syndrome (Hall 1980). To this list other autoimmune diseases, intermittent Cushing's syndrome and other diseases can be added. This observation supports the possibility that even mental disorders which by definition have a recurrent course, like melancholia and bipolar disorder, can be mimicked by somatic diseases.

The nature of the relationship between medical disorders and psychiatric symptoms can be one of the following:

- Causative
- Exacerbating
- Reactive
- Comorbidity

The decision about which of the 4 types listed above is the right one, is by no means easy and must be evaluated in every single case. In epidemiological studies, Hill's criteria of causation can be applied (Hill 1965; Fedak, Bernal, Capshaw et al. 2015). These criteria were originally presented by Austin Bradford Hill (1897-1991), a British medical statistician, and outline the minimal conditions needed to establish a causal relationship between two items.

Kurt Schneider, in his book *Klinische Psychopathologie*, suggests the following obligatory criteria for the identification of a causative relationship (Schneider 1971):

- Significant physical findings
- An evident temporal relationship between physical findings and psychiatric symptoms
- A certain parallelism of the courses of both physical findings and psychiatric symptoms

A more detailed list of criteria for the establishment of a causative relationship can be found in the book of Cardinal and Bullmore (2011). Additional discussion of this important subject is given by Estroff and Gold (Gold and Pottash 1986). Causative physical illness has been found to be a common occurrence. Prevalences of 7.7 and 9.1% were found by two research groups in psychiatric outpatients. In psychiatric inpatients, the prevalence was found to be in the range of 5-43%. In the same chapter they also discuss the reasons of the failure of primary care physicians and psychiatrists to diagnose organic causes of mental problems (McIntyre and Romano 1977).

At the end of this section, we shall make a short detour into the history of endocrine psychiatry and cite some relevant findings from the works of a few important early researchers.

Starting in the 19th century, the association between many physical illnesses/conditions and mental symptoms was observed. The French psychiatrist Paul-Marie Maxime Laignel-Lavastine (1875–1953) was the first to study the relationship between mental problems and endocrine diseases in a comprehensive and scientific way. In 1908, at a congress of the alienists and neurologists of the French-speaking countries in Dijon, he called this new field of study *psychiatrie endocrinienne.* In the years 1908 to 1924 he published more than 30 scientific articles (Bleuler 1954), as well as several books, on the connection of internal secretions and mental illnesses (Steinberg, Kirkby and Himmerich 2015; Laignel-Lavastine 1908,1919,1928, 2015). In these publications, he covers endocrine organs such as the thyroid, parathyroid, gonads, pituitary and the adrenal glands.

The American neurosurgeon Harvey Cushing (1869-1939) had a long-standing interest in the relationship between mental symptoms and endocrine disorders. He wrote: "Psychic conditions profoundly influence the discharges from the glands of internal secretion, but we are on a much less secure footing when we come to the reverse, namely the effect on psyche and nervous system of chronic states of glandular overactivity or underactivity. However,... it is fair to assume that each of the resultant clinical types will exhibit more or less characteristic mental deviations; for the influence of the somatic condition on the mind is certainly as great as that of mind on body" (Cushing 1913). He discovered that an adenoma of the pituitary is the cause of what was later called *Cushing's disease* (Cushing 1932).

Meanwhile, in the German-speaking world, Karl Bonhoeffer (1868-1948), a student of Carl Wernicke and professor of psychiatry and neurology at the Charité in Berlin, published in 1910 the monograph *Die symptomatischen Psychosen* (the exogenous psychoses*)* (Bonhoeffer 1910, 1974). In this work he introduces and discriminates the exogenous psychoses (i.e., those with a somatic etiology; also called secondary or symptomatic psychoses) against the endogenous psychoses (i.e., those with an unknown etiology; also called primary psychoses).

In his book he covers mainly infections and diseases of the inner organs. Regarding endocrine disorders associated with mental symptoms, he mentions hypothyroidism (myxedema), hyperthyroidism (Graves' disease) and hypocortisolism (Addison's disease). About the relationship of Addison's disease, first described by the British physician Thomas Addison in 1849, and mental disorders, Bonhoeffer wrote: "In Addison's disease, certain psychological changes are often, perhaps always, found. The idea that there are similar relationships between the internal secretion of the adrenal glands and the brain as between the thyroid gland and the brain is thus suggested. In particular, hypoplasia of the adrenal cortex observed in disorders of brain development has also made the existence of a close relationship probable."

In Switzerland, Manfred Bleuler (1903-1994), son of Eugen Bleuler and professor of psychiatry at the University of Zürich, had a long-standing interest in the relationship between psychiatry and endocrinology, which culminated in the publication of his monograph *Endokrinologische Psychiatrie* (Bleuler 1954). In this 500-page tome with more than 2,700 literature references, we find a critical account of endocrine psychiatry up to the time of its publication. Bleuler had a decade-long interest in endocrine psychiatry. His main obstacle was the lack of access to a clinical laboratory. Also, before 1954 only very few and crude laboratory methods relevant for the assessment of endocrine disorders were available. Therefore, his findings and conclusions were mainly based on his clinical observations and a

comprehensive study of the relevant literature. However, in his textbook, Manfred Bleuler mentions several findings which are very relevant for the subject under consideration (Bleuler 1954):

- A specific endocrine disorder can cause very different psychopathological pictures
- Different endocrine disorders (even contradictory ones like adrenal hypo- and hyperfunction) can cause the same psychopathological picture
- There is no strong relationship between the severity of the endocrine dysfunction and the observed mental symptoms
- There is no clear temporal relationship between the appearance of mental symptoms and the evolution of an endocrine disorder
- In the case of Cushing's disease/syndrome the course can be periodic with recurrent psychiatric manifestations, thus closely mimicking manic-depressive illness

In 1965 Bleuler published a 30-year retrospection of his work in endocrine psychiatry dedicated to Gabriel Langfeldt, professor of psychiatry at the University of Oslo (Bleuler 1965). Since Bleuler became director of the psychiatric clinic Burghölzli (affiliated with the University of Zürich) in 1942, about 25,000 patients were admitted, whom he and his coworkers investigated also for endocrine disorders. During the previous 30 years, Bleuler had studied more than 6,000 publications related to endocrine psychiatry. Obviously, he had a lot of hands-on experience and, as a Swiss polyglot, a very good knowledge of the relevant literature in different languages. We shall give an English translation of a larger part of this publication containing some important conclusions (Bleuler 1965):

> "Today, it has been possible to arrive at a roughly complete inventory of the mental changes in endocrine patients and of endocrine functions in the mentally ill. We finally know how changes in the hormonal equilibrium affect the psyche. Knowledge of the endocrine effect on the psyche provides a deeper understanding of the mental structure, they allow to grasp biological basic currents of the psychic, a *biological Es*, more clearly than hitherto; they further point to the multiplicity of the influences on the development of the personality; we have understood the preliminary possibilities and limits of endocrine therapy in psychiatric patients and psychiatric therapy in endocrine patients. The review of psychopathology in endocrine diseases was urgent 30 years ago. At that time, we knew only countless confusing individual findings, which often contradicted each other and in some respects gave a distorted picture of reality. False was, among other things, that acromegaly and many other endocrine diseases were accompanied by schizophrenia; there were exaggerated ideas about the degree of specificity of mental symptoms accompanying specific endocrine manifestations, for example, it was often thought that Addison's disease was usually associated only with depression; other misconceptions arose because curiosities were referred to as characteristic conditions, for example intellectual predevelopment at endocrine prematurity. The present knowledge allows us to say clearly and in summary: The psychopathology of endocrine diseases is consubstantial with the psychopathology of brain diseases… The shaping of the picture of the endocrine psychosyndrome in detail does not depend exclusively on the specific type of endocrine disorder, but much more on the personal disposition and constitution,

> the personal development of life and all other than endocrine influences, which are active at the same time. Especially, there is no regular correlation between a certain mood and a certain endocrine disorder. Rather, there is a partial relationship between certain hormonal changes and certain drives. The same endocrine disturbance can lead to the most diverse moods. How little specific the psychopathological endocrine disturbances can be, is drastically illuminated by the fact that opposite endocrine disorders (for example, hyper- and hypofunction of the adrenal cortex) often lead to the same psychopathological pictures). While most endocrine diseases are accompanied by at least mild mental alterations, the statement cannot be reversed: most psychiatric patients are not endocrine ill, but endocrine healthy. The inventory of endocrine findings in psychiatric patients reveals sparse and inconsistent endocrine changes. For decades, it has often been falsely claimed that endocrine findings are regularly found in psychoses. This is not correct - at least judged by the diagnostics available today… It is never possible to make a definitive endocrinological diagnosis with the help of psychopathological findings. The question of how hormones affect the psyche was not answered 30 years ago. Today, the answer is clear and seems almost self-evident: hormones affect the psyche via the brain! They change first functionally and then structurally localized systems in the central nervous system that are specifically tuned to individual hormones."

Fourteen years later, Bleuler contributed an updated 80-page chapter about endocrine psychiatry to the multi-volume series *Psychiatrie der Gegenwart* (Current psychiatry) (Bleuler 1979). It is interesting to note that in Eugen Bleuer's textbook *Lehrbuch der Psychiatrie* (which was edited after his death by his son Manfred) the chapter about endocrine diseases is only 14 pages long, with just a few sentences per disease (Bleuler 1985).

Summary and conclusions

Psychiatrists have been interested in endocrinology for a long time. Associations between many endocrine disorders and mental symptoms were observed by prominent physicians. Unfortunately, up to the middle of the 20th century due to the lack of synthetic hormones, other pharmaceutical treatment options, as well as the paucity of available laboratory methods for a biochemistry-based diagnosis, the field of endocrine psychiatry did not bring it to full bloom. This situation changed for the better with the invention of the radioimmunoassay (RIA) for the quantitative determination of hormones in biological fluids and the maturation of endocrinology. At about the same time, starting in the early 1950s, a first wave of new neuroleptics and antidepressants entered psychiatry and had a profound impact on both therapy and ideas about the etiology/pathophysiology of severe mental disorders. This development gave birth to the age of the neurotransmitters, which is still dominating the field. This, the author believes, is one of the main reasons of the dramatic decline of interest in endocrine psychiatry.

In 1960 the DST was introduced in endocrinology for the diagnosis of Cushing's syndrome (Little 1960). Shortly afterwards, the Australian psychiatrist Bernard Carroll observed that in a majority of patients with severe depression the application of dexamethasone did not suppress the secretion of 11-hydroxycorticosteroids (e.g., cortisol) (Carroll, Martin and

Davies 1968). Further research culminated in the very influential article in the *Archives of General Psychiatry* (Carroll, Feinberg, Greden et al. 1981). In this paper Carroll and colleagues propose the DST for a laboratory-based diagnosis of melancholia. The DST created a lot of excitement and high expectations in the psychiatric community. Within only a couple of years, an enormous number of articles about the DST as a diagnostic tool in psychiatry were published. However, the findings were mixed and a large part of the results did not confirm the earlier findings and claims of Carroll. As explained by Shorter and Fink, Lutz, Healy, Blackwell and Amsterdam, multiple personal and political factors on the level of the individual researchers, the prevailing *zeitgeist*, the dynamics within the psychiatric community and the unfavorable judgement of the American Psychiatric Association (APA) all contributed to the ultimate fall from grace of the DST.

Other, more scientific reasons for the fall of the DST shall be listed and briefly discussed in the following. We should keep in mind that most researchers did not apply the DST as described by Carroll in his 1981 paper. As Helena Kraemer wrote, there *are almost as many DSTs as there are DST studies* (Kraemer 1987). This fact alone points to a severe shortcoming and makes the comparison of the results obtained by different research groups very difficult. The impact of the more technical factors on the performance of the DST will not be addressed in this section (see section "limitations of the DST").

- Sensitivity of the DST

Carroll found a diagnostic sensitivity of the DST in melancholic inpatients of 67%. Most researchers reported significantly smaller sensitivities. Using less stringent diagnostic criteria for the identification of melancholic patients than those of Carroll, like those of the *RDC* and the *DSM-III* (depression with melancholic features) obviously will cause a drop of the sensitivity. Some researchers even understood MDD as a synonym of melancholia, leading to a dilution and substantial reduction of the proportion of real melancholia cases in their patient cohorts. In this sense, the introduction and promotion of the *DSM-III* in 1980 by the APA had a very negative impact on the performance and acceptance of the DST. The use of any etiology-agnostic diagnostic tool with non-validated entities will have a disastrous effect on research in psychiatry and psychopharmacology (Davidson and Gabos-Grecu 2020).

A too high cortisol threshold, a wrong timing (e.g., in the morning) of or only a single cortisol determination will all result in a lower sensitivity of the DST. The use of too little DEX gives rise to false-positive non-suppression. Another very important factor causing artificially high proportions of non-suppressors is a too low post-DEX dexamethasone concentration. This has been observed by multiple researchers and even Carroll himself. However, this important topic never made it into an improved DST. For a valid DST an acceptable range of the dexamethasone concentration (post-DEX) at different times must be defined and the dexamethasone and cortisol concentrations must be determined together at the same time (Meikle 1982).

Another interesting observation is the fact that even in the hands of Carroll, the sensitivity of the DST was only 67%. Why were the remaining third of melancholic patients not also non-suppressors? Obviously, the functionality of their HPA axis was intact, and they did not have a pronounced hypercortisolism. This strongly indicates that the group of patients with melancholia is biologically not homogenous.

The melancholia phenotype, as psychopathologically defined, consists of subgroups with different pathophysiologies (not necessarily different etiologies, as the DST is a state and

not a trait marker). As we have shown above, a melancholia-like clinical picture can be due to many different somatic causes. Among them are autoimmune and endocrine diseases, neoplasms (in particular carcinomas of the pancreas) and infections; in short, anything causing an encephalopathy. As Mark Gold and others have shown, within a cohort of melancholic patients different hormonal axes can be disturbed individually or simultaneously (Extein, Pottash and Gold 1981; Contreras, Menchon, Urretavizcaya et al. 2007). This stresses the importance of a biochemical identification of the different subgroups. The application of a single laboratory test, e.g., the DST, allows for the identification of a biologically more homogenous subgroup of melancholic patients. On the psychopathological level alone, this cannot be achieved. The use of a biomarker (e.g., the DST) provides an additional important element. In biomarker research, this is called *phenotypic anchoring*. Multiple biomarkers/tests can be used for the identification of different homogenous subgroups.

- Specificity of the DST

The specificity of the DST was reported by Carroll as 96%. Zimmerman and Coryell presented in a review the results of 53 studies in which the 1 mg dexamethasone suppression test in normal controls (Zimmerman and Coryell 1987) was applied. A mean rate of non-suppression at 4 pm of 7.4%, and 6.3% at 11 pm was found. However, in 11 (21%) of these studies, the reported rates of non-suppression were higher than 10%. Factors such as recent weight loss, sleep deprivation, psychosocial stress, caffeine use and possibly older age can cause non-suppression in normal controls (Zimmerman and Coryell 1987; Feinberg and Carroll 1984).

Even more disturbing is the observation that elevated rates of non-suppression were found in psychiatric patients with diagnoses other than melancholia. Carroll claimed that the DST is a specific test for the diagnosis of melancholia. In particular, patients with other non-organic forms of depression, like neurotic/reactive depression, should not show non-suppression. However, substantially elevated rates of positive DSTs (i.e., non-suppression) were found also in patient groups like those with personality disorders, schizophrenia, mania, anxiety disorders, post-traumatic stress disorder (PTSD), substance abuse (alcoholism) and dementia (Arana and Mossman 1988; Murphy 1991). Obviously, a hyperactivity of the HPA-axis can have many different causes, even purely psychological ones. This is a well-known fact in psychosomatic medicine and endocrinology.

How shall all these findings be taken into consideration and what is their impact on the applicability of the DST? First, to do justice to Carroll, it must be emphasized that he applied the DST to a very stringently defined patient population and many patients with confounding problems were excluded. Second, the DST was never proposed as a screening test for a broad psychiatric patient population with a wide range of disorders.

The DST should be applied only to a well-defined patient population with severe mood disorders (in the broad sense of Kraepelin's *manic-depressive insanity* [MDI]). Additionally, the current clinical picture should be that of melancholia (Parker and Hadzi-Pavlovic 1996; Taylor and Fink 2006). Other bordering conditions, like mixed states, "schizoaffective disorder" and atypical psychoses could all belong in a certain sense to the MDI fold with a corresponding high proportion of non-suppressors.

Although schizophrenia subtypes are no longer considered in *DSM-5*, schizophrenia is still recognized by many experts to be a very heterogeneous group of disorders. Some of the (old) subtypes, like hebephrenia and schizophrenia simplex, are definitively distinct from

others like paranoid and catatonic schizophrenia. Catatonia has more recently been shown to be a disease in its own right. Therefore, a dissection of the schizophrenia pool should be seriously considered. A part of this "pool" should probably be relabeled as a psychotic mood disorder (Lake 2012, 2021). Therefore, elevated rates of non-suppression in any of the disease groups mentioned above would be no unexpected nor contradicting finding. We should not forget that symptomatic/secondary schizophrenias can have many different somatic causes, not only a hyperactive HPA-axis (Cardinal and Bullmore 2011; Freudenreich 2020).

- Possible applications of the DST

The DST was first proposed as a tool for the diagnosis of melancholia. As the clinical picture of a mental disorder is unspecific and does not allow for the unequivocal identification of its etiology, any additional information strengthening the diagnosis is helpful. Other proposed uses of the DST are the prediction of the response to treatment (ECT or pharmacotherapy with TCAs) (Duval, Mokrani, Monreal, Ortiz et al. 2005), confirmation of a clinical remission, prognosis of relapse, and the prediction of suicide. Additionally, the DST could be helpful with regard to the understanding of the etiology/pathophysiology of mood and psychotic disorders and make an important contribution to the identification of biologically homogenous patient populations.

- Why did psychoendocrinology fail?

Francesca Brambilla, in her review "Psychoneuroendocrinology: a science of the past or a new pathway for the future?" (Brambilla 2000) wrote:

> "Psychoneuroendocrinology is a branch of neuroscience that developed in the beginning of the last century, which investigates the possibility of a cause–effect link between endocrinopathies and mental disorders - with these studies ending in negative results… In a first approach, a cause–effect link between peripheral well-defined endocrinopathies and similar nosographically well-defined psychopathologies was looked for… What was intriguing was the fact that different endocrine imbalances were accompanied by the same types of psychopathologies and, *vice versa*, that the same endocrine imbalance was accompanied by different types of psychopathologies… At this point, the interpretation of the mass of data that were sometimes concordant and sometimes discordant in their immediate meaning, pointing to one or another type of biochemical brain pathology for each mental illness, became a real problem. Doubts started to rise on the consistency and validity of this diagnostic and prognostic approach. Psychoneuroendocrinology did not seem to offer the biochemical "target" for each psychopathology, but, rather, made the history of etiopathogenesis, nosography, prognosis and therapeutic choices of mental disorders so confused and intriguing that authoritative researchers suggested to abandon it, the observed hormonal pathologies being defined as aspecific, casual, nonvalidable, and, in all, insignificant and meaningless for the understanding of the etiopathogenesis of mental disorders."

Another evaluation and outlook of endocrine psychiatry from a French perspective has been published (Duval, Mokrani and Crocq 2013).

Obviously, disappointed expectations and overly simplistic model conceptions contributed significantly to the neglect of psychoendocrinology. No simple one-to-one

relationship between psychiatric disorders and specific endocrine diseases exists. However, the fact that the dysfunction of an endocrine axis can generate very different psychiatric symptoms indicates the importance of further somatic investigations. Of particular importance is the observation that endocrine disorders (in their prodromal or subclinical forms) are often preceded by psychiatric symptoms (sometimes by years). This is also true for other somatic ailments, nutritional deficiencies and intoxications.

Take-home messages

- Hypercortisolism and/or a positive DST is a common finding in severely depressed patients. After remission, the hypercortisolism is, in general, no longer observed.
- The DST as proposed by Carroll has the potential to be greatly improved. After a careful standardization and validation, such an improved DST will be a useful tool with multiple applications in the field of mood disorders.
- Melancholia is a biologically heterogeneous group. The DST identifies only the subgroup with a hyperactive HPA-axis.
- The clinical picture of a psychiatric patient based only on symptoms does not allow for the identification of the underlying etiology/pathophysiology.
- Primary and secondary (symptomatic, somatic, exogenous) mental disorders often cannot be distinguished on the psychopathological level alone.
- Medical diseases can mimic any mental disorder.
- All endocrine diseases and dysfunctions can cause mental symptoms.
- Mental symptoms are frequently the first and only expression of physical diseases and pathological conditions. They can precede the full somatic clinical picture by years.
- Somatic causes of mental disorders are often missed.
- Treatment-resistant psychiatric patients could have a causative somatic disease.
- A targeted treatment of a causative physical disease often results in the remission of the mental symptoms.
- The development of new psychotropic drugs will be greatly facilitated by the use of biologically more homogenous patient groups. The application of biomarkers (e.g., the DST) to psychopathologically well-defined patients allows for the identification of such patient groups.

Quo vadis?

It ain't over 'til it's over.
Lawrence P. “Yogi” Berra

The time has come for a new appreciation of clinical endocrine psychiatry. A close collaboration of psychiatrists and endocrinologists will bear fruit in terms of an increase in knowledge and for the benefit of the patient, especially in the neglected field of women’s mental health.

The DST as proposed by Carroll and colleagues in 1981 was never fully developed, validated and standardized. After such a process, it certainly has the potential to become a useful tool in psychiatry’s armamentarium (Fink 2005). The increase of knowledge in

endocrinology in the last 40 years with regard to the HPA-axis and its disorders, as well as new developments in clinical chemistry and laboratory medicine, could help to generate a new version of the DST on a higher level. In this regard, we would like to mention in particular the LC-MS/MS technology for the quantification of hormones. This also allows for a non-invasive quantification of hormones in saliva (Zhang, Dou, Gu et al. 2013; El-Farhan, Rees and Evans 2017).

In our age of symptom-based psychiatric diagnoses, the DST (and other laboratory tests) could help to initiate a better understanding and discrimination of symptomatic/secondary mental disorders and redirect psychiatrists towards a new appreciation of somato-psychic medicine in general. As psychiatry changed from a brainless (i.e., psychodynamic) to a mindless (i.e., brain-centered) discipline in the last century, it's now time to get back to its roots and become a science of the whole person (including mind, brain and body) again.

As the significant proportion of treatment-resistant cases clearly indicates, a dysfunction of cerebral neurotransmitters can't be the (only) cause of depression. There are many more potential organic causes of severe depressions, a dysfunctional HPA-axis being one of them. Beverley Murphy from the University of Montreal treated depressed patients who were resistant to antidepressants with different antiglucocorticoids and obtained encouraging results (Murphy 1997; Murphy, Ghadirian and Dhar 1998). There is now a substantial number of available drugs for the treatment of hypercortisolism (Tritos and Biller 2018, 2020; Tritos 2021). They work at different targets of the HPA-axis: i. Inhibition of cortisol biosynthesis in the adrenals (e.g., ketoconazole, metyrapone, osilodrostat, mitotane, and etomidate), ii. Pituitary (e.g., cabergoline, pasireotide), and iii. Blocking of the glucocorticoid receptor (mifepristone/RU486). These drugs could be used alone or in combination in cases of severe depression with a biochemically confirmed hyercortisolism and/or a positive DST.

Some of the drugs mentioned above have been used in multiple studies for the treatment of depression with mixed results. Most of these studies are flawed, as the hormone status of the patients with regard to the functionality of the HPA-axis was not determined. Indeed, using a positive DST as an inclusion criterion for such a trial with depressed patients would be very beneficial. One of the major obstacles in current psychotropic drug development is the heterogeneity of the patient populations. In addition to carefully characterized patients on the psychopathology level, a biological test like the DST would enrich the population considerably and make it much more homogenous regarding the underlying pathophysiology. This will enhance the changes of success in the development of new drugs.

References:

Amerio A, Odone A, Marchesi C, Ghaemi SN. Is depression one thing or many? Br J Psychiatry 2014;204(6):488.

Amsterdam J. Comment. Amy S. F. Lutz: The Rise and Fall of the Dexamethasone Suppression Test: Stability, Consensus, Closure. inhn.org.controversies. November 18, 2021.

Arana GW, Baldessarini RJ, Ornsteen M. The Dexamethasone Suppression Test for Diagnosis and Prognosis in Psychiatry. Commentary and Review. Arch Gen Psychiatry 1985,42(12):1193-1204.

Arana GW, Mossman D. The dexamethasone suppression test and depression. Approaches to the use of a laboratory test in psychiatry. Endocrinol Metab Clin North Am 1988;17(1):21-39.

Assad G, Understanding Mental Disorders Due to Medical Conditions or Substance Abuse. What Every Therapist Should Know. Florence: Brunner/Mazel; 1995.

Barsky AJ, Silbersweig DA. Depression in Medical Illness. New York: McGraw Hill Education; 2017, p. 250.

Blackwell B. Comment. Amy S. F. Lutz: The Rise and Fall of the Dexamethasone Suppression Test: Stability, Consensus, Closure. inhn.org.controversies. July 29, 2021.

Bleuler E. Lehrbuch der Psychiatrie (15. Auflage). Berlin: Springer; 1985.

Bleuler M. Endokrinologische Psychiatrie. Stuttgart: Georg Thieme Verlag; 1954.

Bleuler M. Psychiatrie und Endokrinologie - Geschichte ihrer Beziehungen in den letzten dreissig Jahren. Acta Psychiat Scand 1965;41(3):411-18.

Bleuler M. Endokrinologische Psychiatrie. In: Kisker KP, Meyer JE, Müller C, Strömgren E. Psychiatrie der Gegenwart. Zweite Auflage, Band I/1. Berlin: Springer; 1979.

Bonhoeffer K. Die symptomatischen Psychosen im Gefolge von akuten Infektionen und inneren Erkrankungen. Leipzig: Franz Deuticke; 1910.

Bonhoeffer K. Exogenous psychoses. In: Hirsch SR, Shepherd M (Eds.), Themes and Variations in European Psychiatry. Bristol: John Wright; 1974.

Brambilla F. Psychoneurendocrinology: a science of the past or a new pathway for the future? Eur J Pharmacol 2000;405(1-3):341-9.

Brown GM. Neuroendocrine probes as biological markers of affective disorders: new directions. Can J Psychiatry 1989;34(8):819-23.

Bullmore E. The Inflamed Mind: A radical new approach to depression. London: Short Books; 2018.

Cardinal RN, Bullmore ED. The Diagnosis of Psychosis. Cambridge: Cambridge University Press; 2011.

Carney MWP, Roth M, Garside RF. The Diagnosis of Depressive Syndromes and the Prediction of E.C.T. Response. Br J Psychiatry 1965;111(477):659–74.

Carr V, Morris H, Gilliland J. The effect of serum dexamethasone concentrations in the dexamethasone suppression test. Biol Psychiatry 1986;21(8-9):735-43.

Carroll BJ, Martin FI, Davies B. Resistance to suppression by dexamethasone of plasma 11-O.H.C.S. levels in severe depressive illness. Br Med J 1968;3(5613):285-7.

Carroll BJ, Curtis GC, Davies BM, Mendels J, Sugerman AA. Urinary free cortisol excretion in depression. Psychol Med 1976a;6(1):43-50.

Carroll BJ, Curtis GC, Mendels J. Cerebrospinal fluid and plasma free cortisol concentrations in depression. Psychol Med 1976b;6(2):235-44.

Carroll BJ, Feinberg M, Greden JF, Haskett RF, James NM, Steiner M, Tarika J. Diagnosis of endogenous depression. Comparison of clinical, research and neuroendocrine criteria. J Affect Disord 1980; 2(3):177-94.

Carroll BJ, Feinberg M, Greden JF, Tarika J, Albala AA, Haskett RF, James NM, Kronfol Z, Lohr N, Steiner M, de Vigne JP, Young E. A specific laboratory test for the diagnosis of melancholia. Standardization, validation, and clinical utility. Arch Gen Psychiatry 1981;38(1):15-22.

Carroll BJ. The dexamethasone suppression test for melancholia. Br J Psychiatry 1982;140(3):292-304.

Carroll BJ. Dexamethasone Suppression Test. In: Hall RCW, Beresford TP. Handbook of Psychiatric Diagnostic Procedures, Volume I. New York: Medical & Scientific Books; 1984.

Carroll BJ. Dexamethasone suppression test: a review of contemporary confusion. J Clin Psychiatry 1985;46(2 Pt 2):13-24.

Carroll BJ, Cassidy F, Naftolowitz D, Tatham NE, Wilson WH, Iranmanesh A, Liu PY, Veldhuis JD. Pathophysiology of hypercortisolism in depression. Acta Psychiatr Scand Suppl 2007;(433):90-103.

Carroll BJ. Biomarkers in DSM-5: Lost in translation. Aust N Z J Psychiatry 2013;47(7):676–8.

Carroll BJ. Beyond symptom counts to case-wise probabilities. Bipolar Disord 2017;19(5):403-4.

Cassidy F, Ritchie JC, Verghese K, Carroll BJ. Dexamethasone metabolism in dexamethasone suppression test suppressors and nonsuppressors. Biol Psychiatry 2000;47(7):677-80.

Condren RM, Thakore JH. Cushing's disease and melancholia. Stress 2001;4(2):91-119.

Contreras F, Menchon JM, Urretavizcaya M, Navarro MA, Vallejo J, Parker G. Hormonal differences between psychotic and non-psychotic melancholic depression. J Affect Disord 2007;100(1-3):65-73.

Coryell W. The use of laboratory tests in psychiatric diagnosis: the DST as an example. Psychiatr Dev 1984;2(3):139-59.

Cosci F, Fava GA, Sonino N. Mood and anxiety disorders as early manifestations of medical illness: a systematic review. Psychother Psychosom 2015;84(1):22-9.

Cushing H. Psychiatric disturbances associated with disorders of the ductless glands. Am J Insanity 1913;69:965–90.

Cushing H. The basophil adenomas of the pituitary body and their clinical manifestations (pituitary basophilism). Bull Johns Hopkins Hosp 1932;50:137–95.

Cutler J, Marcus E. Psychiatry (2nd edition). Oxford: Oxford University Press; 2010.

Dalmau J, Armangué T, Planagumà J, Radosevic M, Mannara F, Leypoldt F, Geis C, Lancaster E, Titulaer MJ, Rosenfeld MR, Graus F. An update on anti-NMDA receptor encephalitis for neurologists and psychiatrists: mechanisms and models. Lancet Neurol 2019;18(11):1045-57.

David AS, Fleminger S, Kopelman MD, Lovestone S, Mellers JDC. Lishman's Organic Psychiatry: A Textbook of Neuropsychiatry. Oxford: Wiley-Blackwell; 2009.

Davidson M, Gabos-Grecu C. Do DSM classifications help or hinder drug development? Dialogues Clin Neurosci 2020;22(1):73-79.

De Leo M, Cozzolino A, Colao A, Pivonello R. Subclinical Cushing's syndrome. Best Pract Res Clin Endocrinol Metab 2012;26(4):497-505.

Duval F. Endocrinologie et psychiatrie. Encyclopédie Médico-Chirurgicale, Psychiatrie 37-640-A-10. 1-28; 2003.

Duval F, Mokrani M-C, Monreal Ortiz JA, Schulz P, Champeval C, Macher J-P. Neuroendocrine predictors of the evolution of depression. Dialogues Clin Neurosci 2005;7(3):273-82.

Duval F, Mokrani M-C, Crocq M-A. What future for neuroendocrinology in psychiatry? Psychoneuroendocrinology 2013;38(8):1213-19.

El-Farhan N, Rees DA, Evans C. Measuring cortisol in serum, urine and saliva - are our assays good enough? Ann Clin Biochem 2017;54(3):308-22.

Evans DL, Nemeroff, CB. The clinical use of the dexamethasone suppression test in DSM-III affective disorders: Correlation with the severe depressive subtypes of melancholia and psychosis. J Psychiatr Res 1987;21(2):185–94.

Evans DL. Use of the Dexamethasone Suppression Test in Clinical Psychiatry. In: Schatzberg AF, Nemeroff CB, editors. The Hypothalamic-Pituitary-Adrenal Axis: Physiology, Pathophysiology, and Psychiatric Implications. New York: Raven Press; 1988.

Extein I, Pottash ALC, Gold MS. Relationship of thyrotropin-releasing hormone test and dexamethasone suppression test abnormalities in unipolar depression. Psychiatry Res 1981;4(1):49-53.

Extein I, Pottash AL, Gold MS. Number of cortisol time-points and dexamethasone suppression test sensitivity for major depression. Psychoneuroendocrinology 1985;10(3):281-8.

Extein I, Gold MS, editors. Medical Mimics of Psychiatric Disorders. Washington: American Psychiatric Press; 1986.

Fava GA, Sonino N, Morphy MA. Major Depression Associated with Endocrine Disease. Psychiatr Dev 1987;5(4):321-48.

Fava GA, Morphy MA, Sonino N. Affective prodromes of medical illness. Psychother Psychosom 1994a;62(3-4):141-5.

Fava GA. Affective disorders and endocrine disease. New insights from psychosomatic studies. Psychosomatics 1994b;35(4):341-53.

Fava GA. Subclinical symptoms in mood disorders: pathophysiological and therapeutic implications. Psychol Med 1999;29(1):47-61.

Fedak KM, Bernal A, Capshaw ZA, Gross S. Applying the Bradford Hill criteria in the 21st century: how data integration has changed causal inference in molecular epidemiology. Emerg Themes Epidemiol 2015;12:14.

Feinberg M, Carroll BJ. Biological 'markers' for endogenous depression: Effect of age, severity of illness, weight loss, and polarity. Arch Gen psychiatry 1984;41(11):1080-5.

Fink M. Should the dexamethasone suppression test be resurrected? Acta Psychiatr Scand 2005;112(4):245-9.

Fink M, Bolwig TG, Parker G, Shorter E. Melancholia: restoration in psychiatric classification recommended. Acta Psychiatr Scand 2007;115(2):89-92.

Freudenreich O. Psychotic Disorders: A Practical Guide (2nd edition). Cham: Humana Press; 2020 (ch. 5).

Ghaemi SN, Vöhringer PA. The heterogeneity of depression: an old debate renewed. Acta Psychiatr Scand 2011;124(6):497.

Giannini AJ, Black HR, Goettsche RL. Psychiatric, Psychogenic and Somatopsychic Disorders Handbook. A Laboratory and Clinical Guide to the Medical Management of Emotional and Intellectual Pathology. Garden City: Medical Examination Publishing; 1978.

Glassman AH et al. The dexamethasone suppression test: an overview of its current status in psychiatry. The APA Task Force on Laboratory Tests in Psychiatry. Am J Psychiatry 1987;144(10):1253-62.

Goggans FC, Wilson Jr WR, Gold MS, Pottash AL. Effect of multiple time point sampling on the sensitivity of the dexamethasone suppression test. Am J Psychiatry 1983;140(7):909-10.

Gold MS, Pottash ALC. Diagnostic and Laboratory Testing in Psychiatry. New York: Plenum; 1986.

Green, HS, Kane JM. The Dexamethasone Suppression Test in Depression. Clin Neuropharmacol, 1983;6(1):7–24.

Halbreich U, editor. Hormones and Depression. New York: Raven Press; 1987.

Hall RCW, editor. Psychiatric Presentations of Medical Illness: Somatopsychic Disorders. New York: Spectrum Publication; 1980.

Hall RCW, Beresford TP, editors. Handbook of Psychiatric Diagnostic Procedures Vol. I. New York: Spectrum Publication; 1984.

Hall RCW, Beresford TP, Blow FC, Hall AK. Differentiating Physical from Psychiatric Disorders. In: Thase ME, Edelstein BA, Hersen M. Handbook of Outpatient Treatment of Adults: Nonpsychotic Mental Disorders. New York: Plenum Press; 1990.

Healy D. Comment. Amy S. F. Lutz: The Rise and Fall of the Dexamethasone Suppression Test: Stability, Consensus, Closure. inhn.org.controversies. July 15, 2021.

Henley DE, Leendertz JA, Russell GM, Wood SA, Taheri S, Woltersdorf WW, Lightman SL. Development of an automated blood sampling system for use in humans. J Med Eng Technol 2009;33(3):199-208.

Hill AB. The Environment and Disease: Association or Causation? Proc R Soc Med 1965;58:295-300.

Hui SL, Zhou XH. Evaluation of diagnostic tests without gold standards. Stat Methods Med Res 1998;7(4):354-70.

Hunt GE, O'Sullivan BT, Johnson GF, Caterson ID. Effect of high plasma dexamethasone levels on DST sensitivity: dose-response study in depressed patients and controls. Psychiatry Res 1991;36(2):209-22.

Insel TR, Goodwin FK. The dexamethasone suppression test: promises and problems of diagnostic laboratory tests in psychiatry. Hosp Community Psychiatry 1983;34(12):1131-8.

Jefferson JW, Marshall JR. Neuropsychiatric Features of Medical Disorders. New York: Plenum; 1981.

Kannan CR. The Adrenal Gland (Clinical Surveys in Endocrinology, Volume 2). New York: Plenum; 1988.

Kendler KS. The nature of psychiatric disorders. World Psychiatry 2016;15:5–12.

Kendler KS, Engstrom EJ. Dreyfus and the shift of melancholia in Kraepelin's textbooks from an involutional to a manic-depressive illness. J Affect Disord 2020;270:42-50.

Klein HE. Biologische Marker bei affektiven Erkrankungen (Monographien aus dem Gesamtgebiete der Psychiatrie, Band 45). Berlin: Springer Verlag; 1987.

Koranyi EK. Morbidity and rate of undiagnosed physical illnesses in a psychiatric clinic population. Arch Gen Psychiatry 1979;36(4):414-19.

Koranyi EK, Potoczny WM. Physical illnesses underlying psychiatric symptoms. Psychother Psychosom 1992;58(3-4):155-60.

Koranyi EK, Potoczny WM. Physical Illnesses Underlying Psychiatric Symptoms. In: Fava GA, Freyberger H. Handbook of Psychosomatic Medicine. Madison: International Universities Press; 1998.

Kraemer HC. The methodological and statistical evaluation of medical tests: The dexamethasone suppression test in psychiatry. Psychoneuroendocrinology 1987;12(6):411-27.

Kraepelin E. Psychiatrie. Ein Lehrbuch für Studierende und Ärzte. 1. Band, Allgemeine Psychiatrie (8th Ed.). Leipzig: Barth; 1909.

Krishnan KRR, Davidson JR, Rayasam K, Tanas KS, Shope FS, Pelton S. Diagnostic utility of the dexamethasone suppression test. Biol Psychiatry 1987; 22(5):618-28.

Lacroix A, Feelders RA, Stratakis CA, Nieman LK. Cushing's Syndrome. Lancet 2015; 386: 913-27.

Laignel-Lavastine M. Des troubles psychiques par perturbations des glandes à sécrétion interne. Paris: G. Masson; 1908.

Laignel-Lavastine M. The internal secretions and the nervous system. New York: Nervous and Mental Disease Publishing; 1919.

Laignel-Lavastine M. La méthode concentrique dans l'étude des psychonévrosés. Leçons cliniques de la Pitié 1927. Paris: Chahine; 1928.

Laignel-Lavastine M. The Concentric Method in the Diagnosis of Psychoneurotics. London: Routledge; 2015 (first English edition: 1931).

Lake CR. Schizophrenia Is a Misdiagnosis: Implications for the DSM-5 and the ICD-11. New York: Springer; 2012.

Lake CR. Bipolar. London: Academic Press; 2021.

Lanska DJ. Historical aspects of the major neurological vitamin deficiency disorders: the water-soluble B vitamins. In: Finger S, Boller F, Tyler KL, editors. Handbook of Clinical Neurology, Vol. 95 (3rd series). Amsterdam: Elsevier; 2010.

Liebl R. Störfaktoren beim Dexamethason-Hemmtest. Klin Wochenschr 1986;64(12):535-9.

Lindholm J. Cushing's disease, pseudo-Cushing states and the dexamethasone test: a historical and critical review. Pituitary 2014;17(4):374-80.

Linkowski P, Mendlewicz J, Leclercq R, Brasseur M, Hubain P, Golstein J, Copinschi C, Van Cauter E. The 24-hour profile of adrenocorticotropin and cortisol in major depressive illness. J Clin Endocrinol Metab 1985;61(3):429-38.

Lipowski ZJ. To Reduce or to Integrate: Psychiatry’s Dilemma. Can J Psychiatry 1986;31(4):347–51.

Lipowski ZJ. The integrative approach to psychiatry. Aust N Z J Psychiatry 1990;24(4):470-4.

Lishman WA. Organic Psychiatry: The Psychological Consequences of Cerebral Disorder (3rd Ed.). Oxford: Blackwell Publishing; 1997.

Little GW. Tests of pituitary-adrenal suppressibility in the diagnosis of Cushing's syndrome. J Clin Endocrinol Metab 1960;20:1539-60.

Lutz ASF. The Rise and Fall of the Dexamethasone Suppression Test: Stability, Consensus, Closure. inhn.org.controversies. April 15, 2021.

Maguire KP, Schweitzer I, Biddle N, Bridge S, Tiller JW. The dexamethasone suppression test: importance of dexamethasone concentrations. Biol Psychiatry 1987;22(8):957-67.

McCarthy DJ, Corrin KM. Medical Treatment of Mental Disease. The Toxic and Organic Basis of Psychiatry. Philadelphia: JB Lippincott Company; 1955.

McIntyre JS, Romano J. Is there a stethoscope in the house (and is it used)? Arch Gen Psychiatry 1977;34(10):1147-51.

Meikle AW. Dexamethasone suppression tests: usefulness of simultaneous measurement of plasma cortisol and dexamethasone. Clin Endocrinol (Oxf) 1982;16(4):401-8.

Meltzer MY, Fang VS. Cortisol determination and the dexamethasone suppression test. A review. Arch Gen Psychiatry 1983;40(5):501-5.

Mitchell P, Hadzi-Pavlovic D, Parker G, Hickie I, Wilhelm K, Brodaty H, Boyce P. Depressive psychomotor disturbance, cortisol, and dexamethasone. Biol Psychiatry 1996;40(10):941-50.

Moore DP, Puri BK. Textbook of Clinical Neuropsychiatry and Behavioral Neuroscience (3rd edition). London: Taylor & Francis; 2012.

Morris H, Carr V, Gilliland J, Hooper M. Dexamethasone Concentrations and the Dexamethasone Suppression Test in Psychiatric Disorders. Br J Psychiatry 1986;148(1), 66-9.

Morrison J. When Psychological Problems Mask Medical Disorders: A Guide for Psychotherapists (2nd Ed.). New York: The Guilford Press; 2015.

Mortola JF, Liu JH, Gillin JC, Rasmussen DD, Yen SS. Pulsatile rhythms of adrenocorticotropin (ACTH) and cortisol in women with endogenous depression: evidence for increased ACTH pulse frequency. J Clin Endocrinol Metab 1987;65(5):962-8.

Mossman D, Somoza E. Maximizing Diagnostic Information from the Dexamethasone Suppression Test. An Approach to Criterion Selection Using Receiver Operating Characteristic Analysis. Arch Gen Psychiatry 1989;46(7):653-60.

Murphy BE. Steroids and depression. J Steroid Biochem Mol Biol 1991;38(5):537-59.

Murphy BE. Antiglucocorticoid therapies in major depression: a review. Psychoneuroendocrinology 1997;22(Suppl 1):S125-32.

Murphy BE, Ghadirian AM, Dhar V. Neuroendocrine Responses to Inhibitors of Steroid Biosynthesis in Patients with Major Depression Resistant to Antidepressant Therapy. Can J Psychiatry 1998;43(3):279–86.

Nandam LS, Brazel M, Zhou M, Jhaveri DJ. Cortisol and Major Depressive Disorder-Translating Findings from Humans to Animal Models and Back. Front Psychiatry 2020;10:974.

Nelson JC, Davis JM. DST studies in psychotic depression: a meta-analysis. Am J Psychiatry 1997;154(11):1497-1503.

Orth DN. Cushing's Syndrome. N Engl J Med 1995;332(12):791-803.

Oster H, Challet E, Ott V, Arvat E, de Kloet ER, Dijk D-J, Lightman St, Vgontzas A, Van Cauter E. The functional and clinical significance of the 24-h rhythm of circulating glucocorticoids. Endocr Rev 2017;38(1):3-45.

Parker G, Hadzi-Pavlovic D. Melancholia. A Disorder of Movement and Mood. A Phenomenological and Neurobiological Review. Cambridge: Cambridge University Press; 1996.

Parker G, Fink M, Shorter E, Taylor MA, Akiskal H, Berrios G, Bolwig T, Brown WA, Carroll B, Healy D, Klein DF, Koukopoulos A, Michels R, Paris J, Rubin RT, Spitzer R, Swartz C. Issues for DSM-5: whither melancholia? The case for its classification as a distinct mood disorder. Am J Psychiatry 2010;167(7):745-7.

Pereira AM, Tiemensma J, Romijn JA. Neuropsychiatric Disorders in Cushing's Syndrome. Neuroendocrinology 2010;92(suppl 1):65–70.

Pfaff DW, Phillips MI, Rubin RT. Principles of Hormone/Behavior Relations. Amsterdam: Academic Press; 2004.

Pfaff DW, Rubin RT, Schneider JE, Head G. Principles of Hormone/Behavior Relations (2nd Edition). Amsterdam: Academic Press; 2018.

Poland RE, Rubin RT, Lesser IM, Lane LA, Hart PJ. Neuroendocrine aspects of primary endogenous depression. II. Serum dexamethasone concentrations and hypothalamic-pituitary-adrenal cortical activity as determinants of the dexamethasone suppression test response. Arch Gen Psychiatry 1987;44(9):790-5.

Pollak TA, Lennox BR, Müller S, Benros ME, Prüss H, van Elst LT, Klein H, Steiner J, Frodl T, Bogerts B, Tian L, Groc L, Hasan A, Baune BT, Endres D, Haroon E, Yolken R, Benedetti F, Halaris A, Meyer JH, Stassen H, Leboyer M, Fuchs D, Otto M, Brown DA, Vincent A, Najjar S, Bechter K. Autoimmune psychosis: an international consensus on an approach to the diagnosis and management of psychosis of suspected autoimmune origin. Lancet Psychiatry 2020;7(1):93-108.

Ricoux, A, Guitteny-Collas M, Sauvaget A, Delvot P, Pottier P, Hamidou M, Vanelle JM. Troubles psychiatriques induits par la corticothérapie orale: mise au point sur la nature, l'incidence, les facteurs de risque et le traitement. Rev Med Interne 2013;34(5):293–302.

Ritchie JC, Carroll BJ, Olton PR, Shively V, Feinberg M. Plasma cortisol determination for the dexamethasone suppression test: comparison of competitive protein-binding and commercial radioimmunoassay methods. Arch Gen Psychiatry 1985; 42(5):493-7.

Ritchie JC, Belkin BM, Krishnan KRR, Nemeroff CB, Carroll BJ. Plasma dexamethasone concentrations and the dexamethasone suppression test. Biol Psychiatry 1990;27(2):159-73.

Robertson MM, Katona CL, editors. Depression and Physical Illness. Chichester: Wiley; 1997.

Rush AJ, Giles DE, Schlesser MA, Orsulak PJ, Parker CR Jr, Weissenburger JE, Crowley GT, Khatami M, Vasavada N. The dexamethasone suppression test in patients with mood disorders. J Clin Psychiatry 1996,57(10):470-84.

Sachar EJ. Corticosteroids in depressive illness. II. A longitudinal psychoendocrine study. Arch Gen Psychiatry 1967;17(5):554-67.

Sachar EJ, editor. Topics in Psychoendocrinology. New York: Grune & Stratton; 1975.

Sachar EJ, editor. Hormones, Behavior, and Psychopathology. New York: Raven Press; 1976a.

Sachar EJ, Roffwarg HP, Gruen PH, Altman N, Sassin J. Neuroendocrine studies of depressive illness. Pharmakopsychiatr Neuropsychopharmakol 1976b;9(1):11-17.

Sachar EJ. Neuroendocrine dysfunction in depressive illness. Annu Rev Med 1976c;27:389-96.

Sadock BJ, Sadock VA, Ruiz P. Kaplan and Sadock's Comprehensive Textbook of Psychiatry, 2 volumes (10th edition). Philadelphia: Wolters Kluwer; 2017

Sansing LH, Tüzün E, Ko MW, Baccon J, Lynch DR, Dalmau J. A patient with encephalitis associated with NMDA receptor antibodies. Nat Clin Pract Neurol 2007;3(5):291-6.

Scaroni C, Albiger NM, Palmieri S, Iacuaniello D, Graziadio C, Damiani L, Zilio M, Stigliano A, Colao A, Pivonello R, Altogether to Beat Cushing's Syndrome (ABC) study group. Approach to patients with pseudo-Cushing's states. Endocr Connect 2020;9(1):R1-R13.

Schiffer RB, Klein RF, Sider RC. The Medical Evaluation of Psychiatric Patients. New York: Plenum; 1988.

Schildkrout B. Unmasking Psychological Symptoms: How Therapists Can Learn to Recognize the Psychological Presentation of Medical Disorders. Hoboken: Wiley; 2011.

Schildkrout B. Masquerading Symptoms: Uncovering Physical Illnesses That Present as Psychological Problems. Hoboken: Wiley; 2014.

Schneider K. Klinische Psychopathologie (9. Auflage). Stuttgart: Georg Thieme Verlag; 1971, p. 79f.

Shapiro MF, Lehman AF. The diagnosis of depression in different clinical settings. An analysis of the literature on the dexamethasone suppression test. J Nerv Ment Dis 1983;171(12):714-20.

Shorter E. The doctrine of the two depressions in historical perspective. Acta Psychiatr Scand 2007;115(Suppl 433):5–13.

Shorter E, Fink M. Endocrine Psychiatry: Solving the Riddle of Melancholia. Oxford: Oxford University Press; 2010.

Shorter E. Endocrine psychiatry in a historical perspective. In: Martin P, editor. Ban TA, Blackwell B, Gershon S, Martin PR, Wegener G. International Network for the History of Neuropsychopharmacology. INHN 2013 (INHN Historical Record, Volume 1). Cordoba: INHN Publisher, 2020. https://inhn.org/books/textbook/endocrine-psychiatry-in-historical-perspective.html.

Shorter E. The Rise and Fall of the Age of Psychopharmacology. Oxford: Oxford University Press; 2021.

Skaer DH. Depression & Other mental illnesses caused by medical diseases: It's not all in your head. CreateSpace Independent Publishing; 2018.

Sonino N, Fava GA. Psychiatric disorders associated with Cushing's syndrome. Epidemiology, pathophysiology and treatment. CNS Drugs 2001;15(5):361-73.

Steinberg H, Kirkby KC, Himmerich H. The Historical Development of Immunoendocrine Concepts of Psychiatric Disorders and Their Therapy. Int J Mol Sci 2015;16:28841-69.

Taylor MA, Fink M. Melancholia. The diagnosis, pathophysiology, and treatment of depressive illness. Cambridge: Cambridge University Press; 2006.

Taylor RL. Psychological Masquerade: Distinguishing Psychological from Organic Disorders, 3rd Edition. New York: Springer; 2007.

Tsagarakis S, Vassiliadi D, Thalassinos N. Endogenous subclinical hypercortisolism: Diagnostic uncertainties and clinical implications. J Endocrinol Invest 2006;29(5):471-82.

Tritos NA, Biller BMK. Medical Therapy for Cushing's Syndrome in the Twenty-first Century. Endocrinol Metab Clin North Am 2018;47(2):427-40.

Tritos NA, Biller BMK. Advances in the Medical Treatment of Cushing Disease. Endocrinol Metab Clin North Am 2020;49(3):401-12.

Tritos NA. Adrenally Directed Medical Therapies for Cushing Syndrome. J Clin Endocrinol Metab 2021;106(1):16-25.

Ueland GÅ, Methlie P, Kellmann R, Bjørgaas M, Åsvold BO, Thorstensen K, Kelp O, Thordarson HB, Mellgren G, Løvås K, Husebye ES. Simultaneous assay of cortisol and dexamethasone improved diagnostic accuracy of the dexamethasone suppression test. Eur J Endocrinol 2017;176(6):705-13.

Van Cauter E, Refetoff S. Evidence for two subtypes of Cushing's disease based on the analysis of episodic cortisol secretion. N Engl J Med 1985;312(21):1343-9.

Vreeburg SA, Hoogendijk WJ, van Pelt J, Derijk RH, Verhagen JC, van Dyck R, Smit JH, Zitman FG, Penninx BW. Major depressive disorder and hypothalamic-pituitary-adrenal axis activity: results from a large cohort study. Arch Gen Psychiatry 2009;66(6):617-26.

Walker III S. A Dose of Sanity. Mind, Medicine, and Misdiagnosis. New York: John Wiley; 1996.

Whitlock FA. Symptomatic Affective Disorders: A Study of Depression and Mania Associated with Physical Disease and Medication. Sydney: Academic Press; 1982.

WHO. The dexamethasone suppression test in depression. A World Health Organization Collaborative Study. Br J Psychiatry 1987;150:459-62.

Yener S, Tuna G, Kant M, Akis M, Kara O, Kalas B, Baris M, Islekel GH. Assessment of Plasma-Free Cortisol Concentrations by LC-MS/MS in Patients with Autonomous Cortisol Secretion. Horm Metab Res 2021;53(11):752-8.

Zhang Q, Dou J, Gu W, Yang G, Lu J. Reassessing the reliability of the salivary cortisol assay for the diagnosis of Cushing syndrome. J Int Med Res 2013;41(5):1387-94.

Zimmerman M, Coryell W, Pfohl B, Stangl D. Four definitions of endogenous depression and the dexamethasone suppression test. J Affect Disord 1985;8(1):37-45.

Zimmerman M, Coryell W, Pfohl B. The validity of the dexamethasone suppression test as a marker for endogenous depression. Arch Gen Psychiatry 1986a;43(4):347-55.

Zimmerman M, Pfohl B, Stangl D, Coryell W. An American validation study of the Newcastle diagnostic scale. I. Relationship with the dexamethasone suppression test. Br J Psychiatry 1986b;149:627-30.

Zimmerman M, Coryell W. The dexamethasone suppression test in healthy controls. Psychoneuroendocrinology 1987;12(4):245-51.

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