Table 1
ACNP videotape interview January 2001

PSYCHOPARMACOLOGISTS WITH SIGNIFICANT CONTRIBUTIONS

Joseph Knoll

Discoverer: deprenyl, the first selective MAOI-Type B

Pioneer: mesencephalic enhancer regulation

Table 2
ACNP videotape interview January 2001

REVIEWED

history of synthetic mesencephalic enhancers:

deprenyl, a phenlethylamine derived enhancer

BPAP, a tryptamine derived enhancer

DISCUSSED

the place of deprenyl & BPAP in the prevention & treatment of disorders

CURRENT STATUS

of deprenyl in the treatment of depression

Table 3
From melancholia to depression: diagnosis and treatment

*Reviewed: historical development of diagnostic concept of melancholia

*Discussed: pharmacological treatment of depression

*Proposed: methodology for finding the place of deprenyl in the treatment of depression

Table 4
Classification of mental illness in
the writings of Hippocrates (460-377 BC)

*PHRENITIS Acute mental disturbance with fever

*MANIA Acute mental disturbance without fever

*MELANCHOLIA **Chronic mental disturbances characterized by fear or depression and associated with aversion, despondency, sleeplessness, restlessness, irritability, etc.**

***EPILEPSY Mental disturbance associated with seizures

* SCYTHIAN DISEASE Transvestism

Table 5
Galen's (129-199 AC) classification of melancholia in his treatise On Melancholy

MELANCHOLIA

Melancholic Temperament vs. Melancholic Illness

MELANCHOLIC ILLNESS

General Melancholia vs. Brain Melancholia vs. Hypochondriacal Melancholia

Table 6
Robert Burton's (1621) classification of
melancholia in his Anatomy of Melancholia

MELANCHOLIA

Head (brain) Melancholia

Body (general) Melancholia

Hypochondriacal (windy) Melancholia

Table 7
The 14 species' of disease included under melancholia
in Boissier de Sauvage's (1768) nosology

Disturbances of Intellectual Life

MELANCHOLIA

Ordinary Melancholia
Erotomania
Religious Melancholia
Imaginary Melancholia
Extravagant Melancholia
Melancholia Attonita (immobility and silence)
Vagabond Melancholia (intense need of movement)
Dancing Melancholia
Hippanthropic Melancholia
(delusions of being transformed into a horse)
Scythian Melancholia
Melancholia Anglica (wish for dying)
Zoanthropic Melancholia
(delusions of being transformed into an animal)
Enthusiastic Melancholia (the belief of being divinely)
Sorrowful Melancholia

Table 8
The 8 species' of disease included under
Melancholia in William Cullen's nosology

Vesanias: Disturbances of Judgment Without Pyrexia
MELANCHOLIA
1 of 3 disorders of Neuroses
Partial Madness

Imagination that One's Body Is in a Dangerous Condition or that One's Affairs Are in a Desperate State
Imagination that One's Affairs Are in a Prosperous State
Violent Love
Superstitious Fear of Future
Aversion from Motion and from all Offices of Life
Restlessness and Impatience
Weariness of Life
Deception Concerning the Nature of One's Species

Table 9
Melancholia in Heinroth's (1818) classification of mental illness

Thomas Reid (1764)
Faculty of Psychology
HEINROTH

FACULTIES	EXALTATION	**DEPRESSION**	MIXED
Intellect	Paranoia	Dementia	Confusion
	Verrückheit	Blödsinn	Verwirtheit
Emotions	Insanity	**Melancholia**	Delusional M
	Wahnsinn		Wahnsinnige M
Volition	Mania	Abulia	Fright
	Manie	Willenlosigkeit	Scheue

Table 10
Melancholia in Kraepelin's (1883-1913)
classification of mental illness from
the 1st to the 8th edition of his textbook

KRAEPELIN			
EDITION	YEAR	CLASS	ILLNESS
1st	1883	Mental Depression	Melancholia Simplex
			Delusional Melancholia
		Mental Excitements	Melancholia Activa
		Periodic Psychoses	Periodic Melancholia
2nd	1887	Melancholia	Melancholia Activa
			Melancholia Simplex
			Melancholia Attonita
		Periodic Psychoses	Periodic Melancholia
		Delusional Psychoses	Delusional Melancholia
4th	**1891**	**Melancholia**	**Melancholia: episodic illness with full remission between episodes characterized by retardation of movements and thinking**
5th	1896	Periodic Psychoses	Depressive Form
		Involutional Psychoses	Involutional Melancholia
7th	1904	Manic-depressive Insanity	

Table 11
Kurt Schneider's (1920, 1958) classification of depression

Jaspers, 1909, 1913

Development vs. Process

SCHNEIDER, 1920, 1958

DEPRESSION (DEPRESSIVE)

Vital Depression	**Depressive Psychopathy**	**Psychogenic Depression**
disease process	anomaly of personality development	reaction to life event

Table 12
Leonhard's (1957) classification of endogenous depression

ENDOGENOUS DEPRESSION

Polarity

Bipolar vs. Unipolar

UNIPOLAR DEPRESSION

Totality

Pure Melancholia vs Pure Depressions

PURE DEPRESSIONS

Non-participatory vs. Harried vs. Hypochondriacal vs. Self-torturing vs Suspicious

Table 13
Adoption of Kraepelin's (1891) unitary concept
of depression in ICD-10 (1992) and DSM-IV (1994)

DEPRESSION

MORE SEVERE	MORE PROLONGED
Depressive Episode (ICD-10)	*Dysthymia (ICD-10)*
Major Depression (DSM-IV)	*Dysthymia (DSM-IV)*

Table 14
Diagnoses that are covered up in the diagnoses
of “depressive episode” and “major depression”

VITAL DEPRESSION

Corporisation

Disturbance of Vital Balance

Feeling of Loss of Vitality

PURE MELANCHOLIA

depressed mood transforms thinking, emotions & will

PURE DEPRESSIONS

only one (or two) component(s) of the mental apparatus is (are) affected

Non-participatory

Harried

Hypochondriacal

Self-torturing

Suspicious

Table 15
Samuel Tuke's (1813) report on results of treatment in patients with melancholia

YORK RETREAT

Population: 30 Patients with the diagnosis of melancholia

Treatment: *Warm bath & Bodily exercise*

Results: 70% response rate with 65% of full recovery

Table 16
Opium is the treatment of melancholia

KRAEPELIN 1891

Opium in the form of a tincture

Opium cure: Three weeks

Increased from 3 minims to 25 minims with daily increments

Decreased from 25 minims to 0 with daily decrements

Favorable response (estimated): about 50%

Table 17
Developments in the 1950s

- **Introduction of the first antidepressants coincided with:**
- Discovery of monoamine neurotransmitters in the brain
- Shift in emphasis from electrical to chemical neurotransmission in the CNS
- Introduction of the spectrophotofluorimeter

Table 18
History of antidepressant development

1. Iproniazid, a MAOI induced euphoria

whereas

reserpine induced dysphoria

2. Iproniazid increased monoamine levels

whereas

reserpine decreased monoamine levels

3. Imipramine blocked neuronal reuptake NE

Table 19
The first reports on the antidepressant effect
of imipramine and iproniazid

1957

KUHN (1957) – Imipramine

Effective in vital depression

LOOMERS, SAUNDERS & KLINE (1957) – Iproniazid

Effective as a psychic energizer

Table 20
Klerman and Cole's (1865) verification of Kuhn's (1957) findings about the antidepressant effect of imipramine

POOLED ANALYSIS OF 23 STUDIES

1009 Patients

550 imipramine and 459 placebo

Response rate

65% imipramine and 31% placebo

Predictability of response

2 of 3 patients improve

1 of the 2 patients responds to the drug

Table 21
Monoamine oxidase inhibitors

IN SPITE OF THE TENUOUS EVIDENCE THAT INHIBITION OF MAO IS RESPONSIBLE FOR THE THERAPEUTIC EFFECT OF IPRONIAZID IN DEPRESSION SEVERAL MAOIs WERE INTRODUCED IN RAPID SUCCESSION

Ascent: late 1950s

iproniazid, isocarboxazid, nialamide, mebranzine, phenelzine

pheniprazine, tranylcypromine

Descent: early 1960s

hepatotoxicity: iproniazid, pheniprazine

hypertensive crises: tranylcypromine

drug-drug interactions, dietary precautions

Descent could not be reversed by

Selective inhibitors

Type B – deprenyl

Type A – moclobemide (introduced several decades later)

Table 22
Monoamine re-uptake inhibitors

SINCE THE MID-1960s MAUIs DOMINATED THE TREATMENT OF DEPRESSION

DRIVEN BY NEUROPHARMACOLOGICAL THEORY

Non-selective, prevailingly NE re-uptake inhibitors
imipramine, amitriptyline
replaced by
selective NE re-uptake inhibitors
desmethylimipramine, maprotiline,
replaced by
selective 5-HT re-uptake inhibitors
citalopram, fluoxetine, paroxetine, sertraline
supplemented by
non-selective, prevailingly 5-HT re-uptake inhibitor
venlafaxine
and
selective NE re-uptake inhibitor
reboxetine

Table 23
Response rates in the meta-analyses of Davis et al. (1993)
indicate that no longer can one expect
that 2 of 3 patients will respond to treatment

		50% OR GREATER DECREASE IN HAMD TOTAL SCORES	
NAME	CLASS	RESPONSE RATES %	
		Drug	Placebo
Sertraline	SSRI	79	48
Imipramine	NSRI	68	40
Fluvoxamine	SSRI	67	39
Amoxapine	NSRI	67	49
Phenelzine	MAOI	64	30
Moclobemide	MAOI-A	64	24
Fluoxetine	SSRI	60	33
Amitriptyline	NSRI	60	25
Mirtazepine	**NaSSA**	**48**	**20**
Paroxetine	**SSRI**	**45**	**23**

Table 24
National Institute of Health collaborative study on the treatment of adolescents with depression (2004)

Number (of patients) needed to treat (NNT)
to obtain 1 success that would not be obtained by placebo

fluoxetine	4
CBT	12
fluoxetine + CBT	3

Table 25
Adoption of statistical methodology
instead of resolving heterogeneity

- Differential responsiveness to the same antidepressant in patient with melancholia was in keeping with post-Kraepelinian split of unitary depression
- Instead of developing a pharmacologically valid nosology (Freyhan, 1957) a statistical methodology was adopted for the demonstration of effectiveness in pharmacologically heterogeneous populations
- Semi-finished antidepressants were released for clinical use without

  delineation of therapeutic profile

  detection of differential effects

  and

  orientation points for prediction

Table 26
FDA approval for clinical use
and actual effectiveness

FDA APPROVAL

Two studies in which the drug is significantly (P=0.05) superior to placebo

ACTUAL EFFECTIVENESS

Khan, Khan & Brown (2002)

52 studies with 8 antidepressants

reviewed by FDA from 1985-2000

in 48% of the studies antidepressant superior to placebo

Table 27
Statistically significant difference

- Implies that it is legitimate to hypothesize that there is a treatment responsive sub-population within the diagnostic sample.
- Does not imply an effective treatment for a clinically significant proportion of patients in the diagnostic group.
- In case of a 50% response rate to an antidepressant and a 25% response rate to a placebo the chances are that of every 8 patients 4 will respond to treatment, and from the 4 responsive patients 2 respond to the pharmacological action of the drug.
- **Covers up that 4 to 6 from the 8 patients administered the drug may develop iatrogenic effects without any therapeutic benefit.**
- **Without identifying the treatment responsive form of illness, the advantage of treatment with an antidepressant over no treatment are blurred, and the advantages over other treatment remain hidden.**

Table 28
From efficacy to the identification of
the treament responsive form of illness

Conventional (statistical) methodology

consensus-based diagnoses and sensitized rating scales

efficacy studies

New methodology

capability of identifying the treatment responsive population

&

delineating the therapeutic profile of the drug

Table 29
Development of the CODE System

ONE OF THE METHODOLOGIES DEVELOPED FOR THE IDENTIFICATION OF THE TREATMENT RESPONSIVE FORM OF ILLNESS

IS THE

CODE SYSTEM

Set of diagnostic instruments that by specially designed

algorithms can assign a diagnosis from several diagnostic systems simultaneously

Its development began with the recognition that the differential responsiveness to a psychotropic drug within a diagnostic category cannot be explained by genetically determined pharmacokinetic differences

Table 30
The CODE System

EACH INSTRUMENT CONSISTS OF:

- *Set of symptoms ("codes"),* which on the basis of standardized data collection yield diagnoses in all the component diagnostic systems
- *Semi-structured interview*, suitable for the elicitation of all the symptoms in terms of "present" or "absent"
- *Diagnostic decision trees*, which organize symptoms into distinct psychiatric illnesses
- *Differs from other polydiagnostic evaluations* by its capability to provide readily accessible information from the lowest to the highest decision making

Table 31
The four components of CODE-DD

90 items ("code's")

Integrated criteria list
with glossary of definitions

Semi-structured interview
completed in 30-40 minutes with or without computer prompting

25 diagnostic decision trees

Table 32
The classifications on which the 25 diagnostic decision trees of CODE-DD are based

1.	SCHNEIDER	1920	13.	MENDELS	1968
2.	LEONARD	1957	14.	PILOWSKY	1969
3.	ROBINS	1972	15.	PAYKEL	1971
4.	FEIGHNER	1972	16.	FOULDS	1973
5.	SPITZER	1978	17.	WING&AL	1974
6.	DSM-III	1980	18.	RASKIN	1976
7.	ICD-9	1988	19.	POLLITT	1965
8.	LEWIS	1934	20.	KIELHOLZ	1972
9.	HAMILTON	1959	21.	KLEIN	1974
10.	KILOH	1963	22.	WINOKUR	1979
11.	OVERALL	1966	23.	BERNER&AL	1983
12.	KRAEPLIN	1891	24.	TAYLOR&AL	1981

25. COMPOSITE DIAGNOSTIC CLASSIFICATION

Table 33
Reliability studies with CODE-DD

STUDY	MEDIAN ITEM AGREEMENT (%)
1st	87.80
2nd	100.00
3rd	100.00

Table 34
Relationship between major depression and depression in other classifications

DIAGNOSIS	PATIENTS	
	N	%
Major depression	230	100
Vienna Research Criteria	**77**	**33**
(33% could not be diagnosed as depressed)		
Major depression	322	100
Definite depressive illness	**119**	**35**
unmotivated depressive mood		
depressive evaluations		
lack of reactive mood changes		
Probable depressive illness	210	65
(2 out of 3 symptoms)		

(37% qualified for definite DI and 65% for probable DI)

Table 35
Nosologically distinct categories

ANALYSIS OF DATA FROM 522 PATIENTS

Despite of some overlap between diagnoses, the major diagnostic categories in the different classifications are nosologically

distinct

Kraeplin's (1891) depressive state

depressed mood, motor retardation, thought retardation

vs.

Shneider's (1920) vital depression

corproization, disturbance of vital balance, feeling of loss of vitality

The overlap between depressive diagnoses within Leonhard's classification is minimal

Leonhard's (1957) pure melancholia

vs.

Leonhard's (1957) pure depressions

Table 36
Methodological contributions

PSYCHOPHARMACOLOGY

Methodology to study the differential effect of antidepressants by the delineation of the therapeutic profile of drugs

NEUROPSYCHOPHARMACOLOGY

Methodology for the identification of the treatment responsive form of illness

Table 37
Neuropsychopharmacology: bridge between genes and psychiatric nosology

NEUROPSYCHOPHARMACOLOGY

- Links clinical effects with brain structures involved in the mode of action of an antidepressant
- **Currently findings are un-interpretable in pharmacological studies with the employment of the spectrophotofluorimeter, receptor assays and gene expression**
- All primary targets of antidepressants are molecular structures involved in neuronal transmission which are encoded with genes which have been identified
- Any form of depression identified by CODE-DD as responsive to an antidepressant is a suitable end-point for genetic research with the candidate gene approach

Table 38
Potential antidepressants currently in clinical investigations

Dual re-uptake inhibitors

Drugs combining 5-HT re-uptake inhibition with 5-HT_2 / 5-HT_3 antagonism

Corticotropin releasing factor receptor antagonists

Substance P (neurokinin) receptor antagonists

Melatonergic agonists

Compounds modulating glutamatergic neurotransmission

Table 39
Clinical development of deprenyl

Discovery
PHENYLISOPROPYLMETHYLPROPYNYLAMINE
(Knoll, Ecseri, Kelemen, Nievel and Knoll, 1965)
Detection and verification of the antidepressant effect of
RACEMIC SUBSTANCE
Varga, 1965
Varga and Tringer, 1971
(-) – DEPRENYL
Tringer et al., 1971
Mann and Gershon, 1980
Mendlewicz and Youdim, 1983 (MD, RCT)
Quitkin et al., 1984 (AD)
McGrath et al., 1988 (AD, RCT)
Bodkin and Amsterdam, 2002 (MD, RCT)
+
CODE-DD
provides capability for
delineation of therapeutic profile
identification of treatment responsive form of illness
determination of differential effect from other antidepressants

Table 40
(-) BPAP

(-) BPAP

Antagonism of tetrabenazine-induced depression is 130 times greater than that of deprenyl

No clinical study

Table 41
Summary

- Reviewed historical development of diagnostic concept of melancholia
- Discussed pharmacological treatment of depression
- Proposed the employment of a new methodology for the clinical development of BPAP, and further clinical development of deprenyl in the treatment of depression

Table 42
Closing

HAPPY BIRTHDAY!

In your eighties, dare to go independently!

Sapere ande!