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
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)

*PHREMITIS 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

<table>
<thead>
<tr>
<th>FACULTIES</th>
<th>EXALTATION</th>
<th>DEPRESSION</th>
<th>MIXED</th>
</tr>
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<tbody>
<tr>
<td>Intellect</td>
<td>Paranoia</td>
<td>Dementia</td>
<td>Confusion</td>
</tr>
<tr>
<td></td>
<td>Verrückheit</td>
<td>Blödsinn</td>
<td>Verwirtheit</td>
</tr>
<tr>
<td>Emotions</td>
<td>Insanity</td>
<td><strong>Melancholia</strong></td>
<td>Delusional M</td>
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<tr>
<td></td>
<td>Wahnsinn</td>
<td></td>
<td>Wahnsinnige M</td>
</tr>
<tr>
<td>Volition</td>
<td>Mania</td>
<td>Abulia</td>
<td>Fright</td>
</tr>
<tr>
<td></td>
<td>Manie</td>
<td>Willenlosigkeit</td>
<td>Scheue</td>
</tr>
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</table>
Table 10
Melancholia in Kraepelin’s (1883-1913)
classification of mental illness from
the 1st to the 8th edition of his textbook

<table>
<thead>
<tr>
<th>EDITION</th>
<th>YEAR</th>
<th>CLASS</th>
<th>ILLNESS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>1883</td>
<td>Mental Depression</td>
<td>Melancholia Simplex</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Delusional Melancholia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mental Excitements</td>
<td>Melancholia Activa</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Periodic Psychoses</td>
<td>Periodic Melancholia</td>
</tr>
<tr>
<td>2nd</td>
<td>1887</td>
<td>Melancholia</td>
<td>Melancholia Simplex</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Melancholia Activa</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Periodic Psychoses</td>
<td>Periodic Melancholia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Delusional Psychoses</td>
<td>Delusional Melancholia</td>
</tr>
<tr>
<td>4th</td>
<td>1891</td>
<td>Melancholia</td>
<td>Melancholia: episodic illness with full remission between episodes characterized by retardation of movements and thinking</td>
</tr>
<tr>
<td>5th</td>
<td>1896</td>
<td>Periodic Psychoses</td>
<td>Depressive Form</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Involutional Psychoses</td>
<td>Involutional Melancholia</td>
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<tr>
<td>7th</td>
<td>1904</td>
<td>Manic-depressive Insanity</td>
<td></td>
</tr>
</tbody>
</table>
Table 11
Kurt Schneider’s (1920, 1958) classification of depression

Jaspers, 1909, 1913
Development vs. Process
SCHNEIDER, 1920, 1958

DEPRESSION (DEPRESSIVE)

<table>
<thead>
<tr>
<th>Vital Depression</th>
<th>Depressive Psychopathy</th>
<th>Psychogenic Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>disease</td>
<td>anomaly of personality</td>
<td>reaction to life event</td>
</tr>
<tr>
<td>process</td>
<td>development</td>
<td></td>
</tr>
</tbody>
</table>
Table 12
Leonhard’s (1957) classification of endogenous depression

<table>
<thead>
<tr>
<th>ENDOGENOUS DEPRESSION</th>
<th>Polarity</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Bipolar vs. Unipolar</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>UNIPOLAR DEPRESSION</th>
<th>Totality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pure Melancholia vs Pure Depressions</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PURE DEPRESSIONS</th>
<th>Non-participatory vs. Harried vs. Hypochondriacal vs. Self-torturing vs Suspicious</th>
</tr>
</thead>
</table>
Table 13
Adoption of Kraepelin’s (1891) unitary concept of depression in ICD-10 (1992) and DSM-IV (1994)

<table>
<thead>
<tr>
<th>DEPRESSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>MORE SEVERE</td>
</tr>
<tr>
<td>Depressive Episode (ICD-10)</td>
</tr>
<tr>
<td>Major Depression (DSM-IV)</td>
</tr>
<tr>
<td>MORE PROLONGED</td>
</tr>
<tr>
<td>Dysthymia (ICD-10)</td>
</tr>
<tr>
<td>Dysthymia (DSM-IV)</td>
</tr>
</tbody>
</table>
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
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
desmethylinipramine, 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 with a 50% OR GREATER DECREASE IN HAMD TOTAL SCORES.

<table>
<thead>
<tr>
<th>NAME</th>
<th>CLASS</th>
<th>RESPONSE RATES %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sertraline</td>
<td>SSRI</td>
<td>79</td>
</tr>
<tr>
<td>Imipramine</td>
<td>NSRI</td>
<td>68</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>SSRI</td>
<td>67</td>
</tr>
<tr>
<td>Amoxapine</td>
<td>NSRI</td>
<td>67</td>
</tr>
<tr>
<td>Phenelzine</td>
<td>MAOI</td>
<td>64</td>
</tr>
<tr>
<td>Moclobemide</td>
<td>MAOI-A</td>
<td>64</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>SSRI</td>
<td>60</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>NSRI</td>
<td>60</td>
</tr>
<tr>
<td>Mirtazepine</td>
<td>NaSSA</td>
<td>48</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>SSRI</td>
<td>45</td>
</tr>
</tbody>
</table>
Table 24

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>fluoxetine</td>
<td>4</td>
</tr>
<tr>
<td>CBT</td>
<td>12</td>
</tr>
<tr>
<td>fluoxetine + CBT</td>
<td>3</td>
</tr>
</tbody>
</table>
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 treatment 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
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 psychotropie drug within a diagnostic category cannot be explained by genetically determined pharmacokinetic differences.
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

<p>| | | | | | |</p>
<table>
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<tr>
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<tbody>
<tr>
<td>1</td>
<td>SCHNEIDER</td>
<td>1920</td>
<td>13</td>
<td>MENDELS</td>
<td>1968</td>
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<tr>
<td>2</td>
<td>LEONARD</td>
<td>1957</td>
<td>14</td>
<td>PILOWSKY</td>
<td>1969</td>
</tr>
<tr>
<td>3</td>
<td>ROBINS</td>
<td>1972</td>
<td>15</td>
<td>PAYKEL</td>
<td>1971</td>
</tr>
<tr>
<td>4</td>
<td>FEIGHNER</td>
<td>1972</td>
<td>16</td>
<td>FOULDS</td>
<td>1973</td>
</tr>
<tr>
<td>5</td>
<td>SPITZER</td>
<td>1978</td>
<td>17</td>
<td>WING&amp;AL</td>
<td>1974</td>
</tr>
<tr>
<td>6</td>
<td>DSM-III</td>
<td>1980</td>
<td>18</td>
<td>RASKIN</td>
<td>1976</td>
</tr>
<tr>
<td>7</td>
<td>ICD-9</td>
<td>1988</td>
<td>19</td>
<td>POLLITT</td>
<td>1965</td>
</tr>
<tr>
<td>8</td>
<td>LEWIS</td>
<td>1934</td>
<td>20</td>
<td>KIELHOLZ</td>
<td>1972</td>
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<tr>
<td>9</td>
<td>HAMILTON</td>
<td>1959</td>
<td>21</td>
<td>KLEIN</td>
<td>1974</td>
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<tr>
<td>10</td>
<td>KILOH</td>
<td>1963</td>
<td>22</td>
<td>WINOKUR</td>
<td>1979</td>
</tr>
<tr>
<td>11</td>
<td>OVERALL</td>
<td>1966</td>
<td>23</td>
<td>BERNER&amp;AL</td>
<td>1983</td>
</tr>
<tr>
<td>12</td>
<td>KRAEPLIN</td>
<td>1891</td>
<td>24</td>
<td>TAYLOR&amp;AL</td>
<td>1981</td>
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<td></td>
<td><strong>COMPOSITE</strong></td>
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<td>25</td>
<td><strong>DIAGNOSTIC</strong></td>
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<td><strong>CLASSIFICATION</strong></td>
<td></td>
<td></td>
<td><strong>CLASSIFICATION</strong></td>
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Table 33
Reliability studies with CODE-DD

<table>
<thead>
<tr>
<th>STUDY</th>
<th>MEDIAN ITEM AGREEMENT (%)</th>
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<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>87.80</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>100.00</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt;</td>
<td>100.00</td>
</tr>
</tbody>
</table>
Table 34
Relationship between major depression and depression in other classifications

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>PATIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
</tr>
<tr>
<td>Major depression</td>
<td>230</td>
</tr>
<tr>
<td>Vienna Research Criteria</td>
<td>77</td>
</tr>
</tbody>
</table>
(33% could not be diagnosed as depressed)

Major depression

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)
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

<table>
<thead>
<tr>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dual re-uptake inhibitors</td>
</tr>
<tr>
<td>Drugs combining 5-HT re-uptake inhibition with 5-HT(_2) / 5-HT(_3) antagonism</td>
</tr>
<tr>
<td>Corticotropin releasing factor receptor antagonists</td>
</tr>
<tr>
<td>Substance P (neurokinin) receptor antagonists</td>
</tr>
<tr>
<td>Melatonergic agonists</td>
</tr>
<tr>
<td>Compounds modulating glutamatergic neurotransmission</td>
</tr>
</tbody>
</table>
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
Antagonism of tetrabenazine-induced depression is 130 times greater than that of deprenyl
No clinical study
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
HAPPY BIRTHDAY!

In your eighties, dare to go independently!
Sapere ande!