1

MADNESS: FROM PSYCHIATRY TO NEURONOLOGY VIA NEUROPSYCHOPHARMACOLOGY

2

“Madness may be as old as mankind”

Roy Porter: Madness A Brief History. Oxford University Press, Oxford, 2002.

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3

DEVELOPMENTS

THAT

LED TO THE BIRTH OF PSYCHIATRY

William Cullen	**Johann Christian Reil**	**Ernst Feuchtersleben**
Prof. Medicine	**Prof. Medicine**	**Dean Medicine**
Edinburgh	**Halle**	**Vienna**
1772: Neurosis Vesanias	**1808: Psychiatry**	**1845: Psychosis**

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SETTING THE STAGE FOR THE DEVELOPMENT OF PSYCHIATRY AS A MEDICAL DISCIPLINE

Adoption of the "reflex" into psychiatry:

Wilhelm Griesinger
Describes "psychic reflexes" (1843)
Perceives mental activity as "reflex activity"
The Pathology and Therapy of Psychic Illnesses (1845)

5

STRUCTURAL UNDERPINNING OF PSYCHIC REFLEX

Camillo Golgi	*Ramon y Cajal*	*Charles Sherrington*
1883	**1890**	**1896 & 1906**
described multi-polar cells in cerebral cortex	**recognized neuron functional & morphological unit**	**demonstrated synapse: functional site of transmission**

-

6

ADOPTION OF GRIESINGER'S VIEW THAT MENTAL ACTIVITY IS REFLEX ACTIVITY

Carl Wernicke
1899

CLASSIFICATION OF PSYCHOSES

hyperfunctioning, hypofunctioning, parafunctioning in "psychosensory," "intrapsychic," "psychomotor" components of "psychic reflex"

7

THE VISION OF PSYCHIC REFLEX BECOMES REALITY

PAVLOV'S RESEARCH

Pavlov's interest in the "psychic reflex" was triggered by the observation that sham feeding produced gastric secretion in a dog

Ivan Petrovich Pavlov

(1906)

developed a behavioural method that allowed the detection and measurement of salivary secretion in chronic experiments in dogs with a surgical fistula in their parotid glands.

8

METHOD & FINDINGS

PAVLOV

DISCOVERED that any sensory stimulus can become a signal for a specific sensory stimulus if it repeatedly coincides (preceding coincidence) with the specific stimulus;

EXPLAINED finding by opening of new, formerly non-operating path in the brain;

HYPOTHESIZED that "psychic activity" is based on changes in the processing of sensory signals in the brain;

REPLACED the term "psychic reflex" with the term "conditioned reflex" (CR);

RENDERED the built-in potential of the brain for processing signals accessible to study via CR functions:

acquisition
extinction
disinhibition
generalization
differentiation
reversal
retardation
secondary CR formation
CR chain formation

(Ban TA. Conditioning and Psychiatry. Aldine, Chicago, 1964; George Allen & Unwin, London, 1966)

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HUMAN BRAIN

1. **Has the potential to use the corresponding word of a sensory CS as a signal to elicit the CR.**
2. **CRs to verbal signals suppress CRs to sensory stimuli & CRs to sensory stimuli suppress URs.**
3. **CRs in the first (sensory) and the second (verbal) signal systems are based on the same built in potential of the brain.**
4. **Human brain operates mainly with CRs, primarily with verbal signals**
5. **Mental pathology is an expression of an abnormality in the activity of the second signal system.**
6. **CR parameters, such as CR acquisition, CR extinction, provides a means for the study of normal and abnormal functioning in both the first and the second signal system.**
7. **If the underlying physiology of CR functions in the brain would be discovered, and CR functions could be linked to psychopathology, CR parameters could serve as a bridge between the language of psychiatry and the language of brain functioning.**

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PSYCHOPATHOLOGY

SYMPTOM BASED APPROACH TO DISEASE

GALEN
(131-201)

SYMPTOMS FOLLOW THE DISEASE AS SHADOW ITS SUBSTANCE.

Psychopathological symptoms are intimately connected with the pathophysiology of psychiatric disease.

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PSYCHOPATHOLOGY
IS
ONE OF THE TWO DISCIPLINES THAT PROVIDE A FOUNDATION FOR PSYCHIATRY

Karl Jaspers
1909 - 1910

“LIFE HISTORY” AND “PERSONALITY DEVELOPMENT” ARE EXPRESSED IN THE CONTENT OF SYMPTOMS; THE “CASE HISTORY” (DISEASE PROCESS) IS EXPRESSED IN THE FORM OF THE SYMPTOMS: HOW THEY ARE EXPERIENCED BY (PROCESSED IN THE BRAIN OF) THE PATIENT.

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KARL JASPERS
GENERAL PSYCHOPATHOLOGY
1913

PHENOMENOLOGICAL PSYCHOPATHOLOGY

Aristotelian distinction between "form" and "content" is adopted for the detection of psychopathology and differentiation among psychiatric diseases.
In different disease processes the "subject"(the patient) is presented in different "forms" (of psychopathologic symptoms) the same "content."

CONTENT
the subject matter patient talks about
FORM
how the patient talks

SOMATIC (HYPCHONDRIACAL) COMPLAINTS (CONTENT)
perceived in the
FORM
of
BODILY HALLUCINATIONS
OBSESSIVE IDEAS
HYPOCHONDRIACAL DELUSIONS

13

HEIDELBERG SCHOOL OF PSYCHIATRY
(1918-1933)

Kurt Wilmanns, Hans Gruhle, Wilhelm Mayer-Gross

Phenomenological Analysis Yielded

VOCABULARY

for a
language of psychiatry

WORDS

from
pathologies of "symbolization" ("condensation." "onematopoesis")
to
pathologies of "psychomotility" ("ambitendency," parakinesis")

DISTINCTIONS

"dysphoria" vs "dysthymia,"
"psychomotor retardation" vs "psychomotor inhibition"

SYMPTOMS & DIAGNOSES

tangential thinking - schizophrenias
circumstantial thinking – dementias
rumination -depressions

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PSYCHOPATHOLOGY & NOSOLOGY

PSYCHOPATHOLOGY
(1 of 2 disciplines that provide a foundation for psychiatry)

symptoms & signs of psychiatric disease

NOSOLOGY
(1 of 2 disciplines that provide a foundation for psychiatry)

how diseases are derived
&
classification of diseases

CLASSIFICATIONS
denominations & qualifications.

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THE ORIGIN OF PSYCHIATRIC NOSOLOGY

BOISSIER DE SAUVAGE
Nosologia Methodica
1768

The emphasis in **disease** is on *homogeneity that each patient in a diagnostic group in terms of symptoms is similar to each other and different from patients in any other diagnostic group*;
The emphasis in a **class of disease** is on shared essential characteristics, i.e., *predictability of outcome and responsiveness to external factors*.

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NOSOLOGY: ORGANIZING PRINCIPLES

1. UNIVERSAL (TOTAL) VS PARTIAL INSANITY

19th century

***William Cullen* (1772)**

Mania (Universal)	**vs**	**Melancholia (Partial)**
***Pinel* (1801)**	***Esquirol* (1838)**	***Kahlbaum* (1864)**
Mania vs. Monomania	**Mania vs. Monomania**	**Vesanias vs.Vecordias**

”

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NOSOLOGY: ORGANIZING PRINCIPLES

DISEASE

is a process that has a natural history of its own and runs a regular predictable course

Thomas Sydenham ***Emil Kraepelin***
1682
1899

2.EPISODIC VS CONTINUOUS COURSE

ENDOGENOUS PSYCHOSES

MANIC DEPRESSIVE INSANITY **DEMENTIA PRAECOX**
episodic with full remissions **continuous deteriorating**
episodic without full remissions

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NOSOLOGY: ORGANIZING PRINCIPLES

3.POLARITY

Karl Leonhard
1957

Classification of Endogenous Psychoses

UNIPOLAR (MONOMORPH) VS BIPOLAR (POLYMORPH)

UNIPOLAR

Pure Mania
Pure Melancholia
Pure Euphorias
Pure Depressions
Systematic Schizophrenias
(paraphrenias, hebephrenias, catatonias)

BIPOLAR

Manic Depressive Psychosis
Cycloid Psychoses
excited/inhibited confusion psychosis
anxiety/happiness psychosis
hyperkinetic/akinetic motility psychosis
Unsystematic Scizophrenias
Cataphasia
Affect-laden paraphrenia

Periodic catatonia

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NEUROPSYCHOPHARMACOLOGY
Studies relationship between neuronal and mental events

Birth of Neuropsychopharmacology

PSYCHOTROPIC DRUGS (1949 – 1957)
NEUROTRANSMITTERS IN THE BRAIN (1950 – 1957)
SPECTROPHOTOFLUORIMETER (1955)

Bernard Brodie	***Alfred Pletscher***
NIH	**NIH**

1955 Decrease in brain serotonin levels after the administration of reserpine, a substance that was seen to induce depression
1956 Increase in brain serotonin levels after the administration of iproniazid (MAOI) that was reported to induce euphoria

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SHIFT FROM THE LANGUAGE OT PSYCHIATRY TO THE LANGUAGE OF PHARMACOLOGY

Abraham Wikler (1957)

The Relation of Psychiatry to Pharmacology (Williams & Wilkins 1957)

Information about the mode of action of drugs lead to an understanding of the biochemical underpinning of mental illness and the development of rational pharmacological treatments.

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TREATMENT WITH PSYCHOTROPIC DRUGS FOCUSED ATTENTION ON THE PHARMACOLOGICAL HETEROGENEITY WIHIN DIAGNOSES

(Thomas A. Ban: *Psychopharmacology*. Williams & Wilkins, Baltimore 1969)

TO OVERCOME THE DIFFICULTIES
FOR THE DEMONSTRATION OF THERAPUTIC EFFICACY
THE RANDOMIZED CLINICAL TRIAL (RCT) WAS ADOPTED

THE REPLACEMENT PROTOTYPE OR NOSOLOGY BASED DIAGNOSES BY
CONSENSUS-BASED DIAGNOSES
AND
PSYCHOPATHOLOGY BY SENSITIZED RATING SCALES
PRECLUDED THE POSSIBILITY
OF
IDENTIFYNG
PHARMACOLOGICALLY HOMOGENEOUS POPULATIONS ON THE BASIS OF
PSYCHOPATHOLOGY & PSCHIATRIC NOSOLOGY

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BIOLOGICAL MEASURES

Robert Kendell **(1984)**

Biological measures have not been shown to be anything more than epiphenomena of mental illness

Thomas Ban **(1987)**

By the mid-1980s it has become evident that there is a "clinical prerequisite" for rendering findings with biological measures interpretable

(Prolegomenon to the Clinical Prerequisite: Psychopharmacology and the Classification of Mental Disorders. Progress in Neuro-Psychopharmacology and Biological Psychiatry 1987; 11: 527-80)

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DISCOVERING THE NEED FOR PSYCHOPATHOLOGY & PSYCHIATRIC NOSOLOGY FOR THE INTERPRETATION OF FINDINGS WITH PSYCHOTROPIC DRUGS

FRANK FISH

The influence of the tranquilizer on the Leonhard schizophrenic syndromes. (Encephale 1964; 53: 245-249)

SCHIZOPHRENIA
474 patients

Marked to Moderate Response to Phenothiazine "tranuilizers"

UNSYSTEMATIC SCHIZOPHRENIAS	SYSTEMATIC SCHIZOPHRENIAS
79% of 123	**23% of 351**
Affect-laden Paraphrenia	**Systematic Hebephrenias**
84.4% from 51	23% of 100
More than 4 in 5	**Less than 1 in 4**

Diagnoses were based on Leonhard's Classification of Endogenous Psychoses. Patients were assigned to the different forms and sub-forms of unsystematic and systematic schizophrenia with the use of Fish's guide to Leonhard's classification of chronic schizophrenia (Psychiatric Quarterly 1964; 38: 438-50).

24

GUIDE AND ALGORTHM TO LEONHARD'S CLASSIFICATION

1982

GUIDE TO LEONHARD'S CLASSIFICATION

(Ban: Comprehensive Psychiatry 1982; 23: 155-165)

1987

DCR BUDAPEST NASHVILLE IN THE DIAGNOSIS AND CLASSIFICATION OF FUNCTIONAL PSYCHOSES

A composite of Leonhard's diagnostic concepts of endogenous psychoses; French & German diagnostic concepts of delusional psychoses and development; and the Scandinavian diagnostic concept of reactive psychoses

[Petho and Ban in collaboration with Kelemen, Ungvari, Karczag, Bitter, Tolna (Budapest), Jarema, Ferrero, Aguglia, Zurria & Fjetland (Nashville). Psychopathology.1987; 21: 153-239].

25

FINDINGS IN THE SCHIZOPHRENIAS

The significantly different response to neuroleptics ("tramquilizers') by Fish in 1964 in the two classes of schizophrenia applies also to adverse effects

TARDIVE DYSKINESIA
International Survey
768 Chronic Schizophrenic Patients

TARDIVE DYSKINESIA

UNSYSTEMATIC SCHIZOPHRENIAS	SYSTEMATIC SCHIZOPHRENIAS
4.3%	**13.3%**
(Fish: 79% response rate)	**(Fish: 23% response rate)**

The inverse relationship found between therapeutic effects and TD indicates that the functional state of the structures involved in the mode of action of neuroleptics is different in the "systematic schizophrenias" from the "unsytematic schizophrenias."

(Guy, Ban & Wilson: An international survey of tardive dyskinesia. Progress in Neuropsychopharmacology & Biological Psychiatry 1985; 9: 401 - 5).

26

POLYDIAGNOSTIC EVALUATION OF DEPRESSIVE & HYPERTHYMIC DISORDERS

The first Composite Diagnostic Evaluation Systems include diagnostic concepts from Emil Kraepelin to the DSM-III-R/DSM-IV

1989

CODE-DD (Thomas Ban)
Composite Diagnostic Evaluation of Depressive Disorders
Ban (English original), JM Productions
Aguglia (Italian). Liviana
Puzynsky, Jarema & Vdoviak (Polish) Prasowa Zaklady

1992

Ferrero, Crocq, Dreyfus (French) Medicine & Hygiene
Laane, Vasar, Aluoja & Loskit (Estonian) Tartu Ulikool

1998

CODE-HD (Peter Gaszner & Thomas Ban)
Composite Diagnostic Evaluation of Hyperthymic Disorders
Gaszner & Ban (English), Animula)

27

FINDINGS WITH CODE-DD

DSM-III-R: MAJOR DEPRESSION

322/233 patients (2 studies)

Number (and percentage) of the 322/233 patients fulfilling criteria of depressive illness in a selected number of classifications included in CODE-DD

COMPOSITE DIAGNOSTIC CLASIFICATION (Ban)
322 patients
unmotivated depressed mood, depressive evaluations & lack of reactive mood changes
119 (37%)

VIENNA RESEARCH CRITERIA (Berner et al)
ENDOGENOMORPHIC DEPRESSIVE/DYSPHORIC AXIAL SYNDROMES
233 patients
depressed/irritable mood, and circadian and sleep disturbances
77 (35%)

KURT SCHNEIDER'S VITAL DEPRESSION
233 patients
corporization, disturbance of vital balance, and feeling of loss of vitality
45 (14%)

EMIL KRAEPELIN'S DEPRESSIVE STATES: 95 ((29.5%)
233 patients
depressed mood, motor retardation, thought retardation
45 (28.5%)

The consensus-based diagnostic concept of "major depression" covers up its component diagnoses.

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DEVELOPMENT OF NOSOLOGIC HOMOTYPING

Ban 2002

BY THE DAWN OF THE 21st CENTURY

1. **molecular genetics entered neuropsychopharmacology and *all genes encoding the primary targets of psychotropic drugs in the brain were identified;***
2. **it was recognised that any treatment responsive population could serve as a reference point for genetic hypotheses for mental illness with the employment of the candidate gene approach.**
3. **Nosologic homotyping is based on "*structural psychopathology*" in which Carl Wernicke's three components of the "psychic reflex" are replaced by three "psychic structures."**
4. ***Nosologic homotypes are identical in psychopathological symptoms and , assigned the same position in the "nosologic matrix,"* based on three nosologic organizing principles.**
5. **Nosologic homotypes are more homogeneous populations in psychopathological symptoms than populations identified by any other method.**

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STRUCTURAL PSYCHOPATHOLOGY
Gyula Nyiro (1958, 1962)

STRUCTURES
Ontogenetic Model

afferent-cognitive	**central-affective**	**efferent-adaptive**
6		automatisms .
5. abstract ideation	ethical, social emotions	voluntary movements
4. concrete ideation	intellectual emotions	echo phenomena
3. image formation	vital emotion	emotional stereotypes
2. differentiated perception	sensorial emotions	incoordinated movements
1.diffuse sensation	undifferentiated signa	simple reflexesl

Each level is functionally connected within and across structures with each other; psychopathologic symptoms arise from the abnormalities in the connections between the different levels within and across structures.

30

THE CONDITIONED REFLEX REVISITED

Clinical Research

1958

STRUCTURAL PSYHOPATHOLOGY

The functional connections between the different levels within & across each structure" are CR connections regulated by differential inhibition within and retarded inhibition across structures.

(Nyiro Gy. The structural aspect of mental processing on the basis of reflex mechanisms. In: Ggesi Kiss P, Kardos L, Lenard F, Molnar I, eds. Studies in Psychology (Pszichologiai Tanulmanyok). Budapest: Akademia: 1958, pp. 265-77).

1961

DIAGNOSTIC TEST PROCEDURE

To study the relationship between clinical diagnoses and CR functions and measure changes in the course of treatment

(Ban TA, Levy L. Physiological patterns: A diagnostic test procedure based on the conditioned reflex method. Journal of Neuropsychiatry 1961; 2: 228-31).

1962

SCHIZOPHRENIA

Clinical research has indicated impairment of "internal inhibition" (CR inhibition & differentiation) in schizophrenia

(Astrup C. Schizophrenia Conditional Reflex Studies. Springfield: Thomas; 1962).

1970

TEST BATTERY

(Ban TA, Lehmann HE, Saxena B. A conditioning test battery for the study of psychopathological mechanisms and psychopharmacological effects. Canadian Psychiatric Association Journal 1970; 15: 301 – 8).

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THE CONDITIONED REFLEX REVISITED

Basic Research

1969

JOSEPH KNOLL recognized that the *cerebral cortex* with its 10 billion neurons with its one million billion connections *has the capacity to accommodate the steadily growing new CR connections throughout life*
(Knoll J.The Theory of Active Reflexes. An Analsis of Some Fundamental Mechansms of Higher Nervous Activity. Budapest: Hungarian Academy of Scienes; 1969)

1970

HOLGER HYDEN recognized that at birth only about 5% to10% of the genome is active, and the rest of *the gene areas can be activated by external factors,* and has shown that external factors, e.g., sensory stimulation give rise to *increased synthesis of mRNA, when learning (conditioning) is involved.*
(Hyden H.The question of molecular basis of memory trace. In: Broadbent DE, editor. .Biology of Memory.New York: Academic Press; 1970),.

1981

ERIC KANDEL found that while the architecture of behaviour, the neuronal circuits of the brain has remain constant, i.e., the same cells invariably hook up with the same cells, the *strength of synaptic connections is getting stronger with learning (CR acquisition) and weaker with habituation (CR extinction*), and has shown the *neuronal circuits of classical conditioning*
(Karen TJ, Walters ET, Kandel ER. Classical conditioning in a simple withdrawal refelex in Aplysis Californica. Journal of Neuroscience 1981; 1: 1426-37).

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MOLECULAR GENETICS – CONDITIONING - PSYCHOPATHOLGY

1. **In the 1980s the possibility was raised that CR formation, the opening up of new, formerly non-operating paths as well as the different CR functions are genetically controlled If this would be the case, with further understanding of the genetics of conditioning, CR-functions such as CR acquisition, CR extinction, delay, etc, conditioning could provide a bridge between molecular genetics and mental functioning.**
   (Ban TA, Guy W. Conditioning and learning in relation to disease. Activ Nerve sup 1985; 27: 236-44)

2. **In spite of the progress in discovering the biology of the CR, it still remains to be established how normal and abnormal mental functioning translate into CR variables.**

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FROM PSYCHIATRY TO NEURONOLOGY

Since the time of its inception the language of psychiatry has been continuously changing, to reflect changes in the conceptualization of insanity

GRIESINGER'S	FEUCHTRSLEBEN'S	CULLEN'S	REIL'S
Psychic Reflex	***Psychosis***	***Neurosis***	***Psychiatry***
today	**today**	**today**	**today**
Conditioned Reflex	***Severe mental illness***	***Dismissed***	***anachronistic***

With the changes in the conceptualization of mental illness time has come to replace the term "psychiatry."

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NEURONOLOGY

One possible term for consideration to replace the term

PSYCHIATRY
is
NEURONOLOGY

Reflect current perception of *psychiatric diseases* as
functional neuronal abnormalities
and
distinguish *psychiatric diseases*
from
neurological diseases
related to *structural changes in the brain.*

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While the language of psychiatry has been changing to keep up with the changes of our conceptualization of mental disease

ROY PORTER'S
contention in 2002 that
"Madness may be as old as mankind"

has remained just as true today as

JEAN-MARTIN CHARCOT'S
contention in 1877 that

"Disease is from of old there has always been and nothing about it changes; it is we who change, as we learn to recognize what was formerly imperceptible"