Jacques-Joseph Moreau de Tours
(1804-1884)

His dream to use drugs in the study of mental disorders became a realistic goal in the mid-20th century with the introduction of effective drugs for mental illness and the spectrophotofluorimeter.
SPECTROPHOTOFUORIMETER (1957)
Capability to measure changes in the concentration of neurotransmitter monamines

NEUROPHARMACOLOGY
Studies the mode of action of centrally acting drugs

NEUROPSYCHOPHARMACOLOGY
Studies the relationship between neuronal and mental events with the use of centrally acting drugs
Studying the mode of action of psychotropic drugs with known therapeutic effects could possibly generate information on the biochemical basis of mental disorders that would guide the development of rational drug treatment and provide the key for bridging the gap between neuronal and mental events.
PROGRESS IN NEUROPSYCHOPHARMACOLOGY 
depends on a continuous dialogue between basic scientists and clinicians

Silvio Garattini
Organization of 1st international Symposium 1957

Ernst Rothlin
Founding president CINP 1957 - 1960

Nathan Kline
Chairman 1st WPA symposium 1957
CHLORPROMAZINE
Development

1937  Bovet  synthesis of first antihistaminic drugs
1949  Laborit  potent sedating effect of promethazine
1950  Guiraud & David  promethazine controls agitation
1951  Charpentier et al  synthesis of CPZ (Dec.11)
1952  Laborit et al  recognition of potential use in psychiatry
1952  Hamon et al  1st patient successfully treated (Feb. 22)
1952  Delay & Deniker  trials at Saint-Anne’s start (March 24)
1952  Delay & Deniker  set the stage for introduction (6 papers)
1952  France  Largactil released for use (November)
1953  Other countries  spread around the world (1953-56)
Henri Laborit
Using it 1st & recognizing its potential for psychiatry

Pierre Deniker
Introducing it into psychiatry & demonstrating its influence on the clinical course of psychosis

Heinz Lehmann
Bringing its full practical significance to the attention of the medical community
Daniel Bovet
Nobel Prize in Medicine 1957

Synthesis of first antihistaminics and identification of curare alkaloids
# RESERPINE

(Rauwolfia serpentina, the snakeroot plant of Ayurvedic medicine)

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Contribution</th>
</tr>
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<tbody>
<tr>
<td>1949</td>
<td>Rustom Vakil</td>
<td>publication on antihypertensive effect</td>
</tr>
<tr>
<td>1952</td>
<td>(Rhone Poulenc)</td>
<td>development &amp; release of CPZ for clinical use</td>
</tr>
<tr>
<td>1952</td>
<td>Mueller, Schlittler &amp; Bein</td>
<td>isolation of reserpine from Rauwolfia root</td>
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<tr>
<td>1953</td>
<td>Hakim</td>
<td>Rauwolfia preparations in schizophrenia</td>
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<tr>
<td>1954</td>
<td>Delay et al</td>
<td>effective in mental disorders</td>
</tr>
<tr>
<td>1954</td>
<td>Kline</td>
<td>effective in mental disorders</td>
</tr>
<tr>
<td>1954</td>
<td>Noce, William &amp; Rapoport</td>
<td>effective in mental disorders</td>
</tr>
<tr>
<td>1954</td>
<td>Weber</td>
<td>comparable to CPZ in action</td>
</tr>
<tr>
<td>1954</td>
<td>Steck</td>
<td>comparable to CPZ in producing EPS</td>
</tr>
<tr>
<td>1954</td>
<td>Freis</td>
<td>Reserpine may induce depression</td>
</tr>
<tr>
<td>1955</td>
<td>Mueller et al</td>
<td>Rauwolfia serpentina may induce depression</td>
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</tbody>
</table>
RESERPINE
Albert Laskar Award
1957

Rustom Vakil
Producing a document that brought Rauwolfia alkaloids into Western medicine

Nathan Kline
Bringing to the attention the value of reserpine in the treatment of nervous and mental disorders

Robert Noce
Recognizing the potential use of reserpine in the mentally defective
After one-year large scale use of CPZ & reserpine Brill and Patton in 1957 reported a population fall in New York State Mental Hospitals
Selects dibenzazepine with closest structural & pharmacological resemblance to CPZ from Geigy’s chemical library; his expectation to find a clinically similar compound to CPZ was not fulfilled

(1956 January 18) notes favorable effects with the substance in a woman with endogenous depression

(1957 August 31) the first article on the antidepressant effect of the substance appears in the Swiss Medical Journal; (September 6) presents paper on the antidepressant effect of the substance (based on the treatment of 43 patients) at WPA congress; drug is released for clinical use in Switzerland with the generic name of imipramine and the trade name of Tofranil
<table>
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<tr>
<th>Year</th>
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<th>Contribution</th>
</tr>
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<tbody>
<tr>
<td>1937</td>
<td>Blaschko</td>
<td>Identification of MAO in tissues</td>
</tr>
<tr>
<td>1937</td>
<td>Pugh &amp; Quastel</td>
<td>Identification of MAO in brain</td>
</tr>
<tr>
<td>1938</td>
<td>Zeller</td>
<td>Differentiation of MA, the enzyme responsible for the deamination of monoamines from DAO</td>
</tr>
<tr>
<td>1951</td>
<td>Herbert Fox</td>
<td>Synthesis of iproniazid</td>
</tr>
<tr>
<td>1952</td>
<td>Selikoff et al.</td>
<td>Iproniazid induces euphoria and overactivity in some tubercular patients</td>
</tr>
<tr>
<td>1952</td>
<td>Flaherty</td>
<td>Iproniazid induced euphoria in a patient</td>
</tr>
<tr>
<td>1952</td>
<td>Zeller et al</td>
<td>Iproniazid inhibits the activity of MAO</td>
</tr>
<tr>
<td>1957</td>
<td>Crane</td>
<td>Iproniazid is an antidepressant</td>
</tr>
<tr>
<td>1957</td>
<td>Loomers et al.</td>
<td>Iproniazid is an antidepressant</td>
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INSTRUMENTAL TO THE DEVELOPMENT OF NEUROPHARMACOLOGY:

1953 Twarog & Page: demonstration of 5HT in the brain
1954 Vogt: demonstration of NE in the brain
1955 Bowman, Caulfield and Udenfriend: introduction of spectrophotofluorimeter

Instrument with a resolution power to detect drug-induced changes in the concentration of monoamine neurotransmitters

Alfred Pletscher  
Parkhurst Shore  
Bernard Brodie

Laboratory of Brodie at the NHI, USA
FINDINGS IN THE SERIES OF KEY EXPERIMENTS THAT WERE TO BECOME THE FOUNDATION OF NEUROPSYCHOPHARMACOLOGY

1955 Pletscher, Shore & Brodie: decrease in brain 5HT after the administration of reserpine, a substance that can induce depression (sed.& cholinergic stim.)

1956 Pletscher: increase in brain 5HT after the administration of iproniazid, a substance that can induce euphoria

1956 Besendorf & Pletscher: increase in brain 5HT after the administration of iproniazid

1956 Brodie, Pletscher & Shore: only those Rauwolfia alkaloids that deplete 5HT have sedative action

1956 Brodie, Pletscher & Shore: 5HT has a role in brain function and reserpine’s action

1956 Pletscher, Shore & Brodie: pre-treatment with iproniazid attenuates reserpine-induced depletion of 5HT

1956 Holzbauer and Vogt: decrease in brain NE after the administration of reserpine

1957 Carlsson et al: pre-treatment with iproniazid prevents reserpine-induced depletion of catecholamines

1957 Pletscher: benzoquinolizines with sedative action release and deplete 5HT
IT WAS ON THE BASIS OF FINDINGS IN THIS SERIES OF EXPERIMENTS TOGETHER WITH PRIOR REPORTS ON THE MONOAMINE OXIDASE INHIBITING (Zeller et al 1952) & MOOD LIFTING EFFECT OF IPRONIAZID (Flaherty 1952; Selikoff et al 1952) and MOOD DEPRESSANT EFFECT OF RESERPINE (Freis 1954; Mueller et al 1955)

THAT IN 1957, A NEW DISCIPLINE NEUROPSYCHOPHARMACOLOGY WAS BORN
SLOW PROGRESS IN THE YEARS THAT FOLLOWED
in establishing relationships between neuronal and mental events

POSSIBLE REASONS OF SLOW PROGRESS

TENUOUS RELATIONSHIPS
BETWEEN

BIOCHEMICAL CHANGES AND CLINICAL EFFECTS
in the initial series of experiments

MAO INHIBITION AND ANTIDEPRESSANT EFFECT
Salzer and Lurie in 1953 & 1955 reported on the antidepressant
effect of isoniazid, the parent substance of iproniazid that has
virtually no MAO inhibiting properties.

MONOAMINE DEPLETION AND MOOD DEPRESSANT EFFECT
Davies and Shepherd in 1955 reported that reserpine improved depression in
their clinical trial.

However tenuous the relationships between elation and monoamine oxidase
inhibition, and depression and monoamine depletion are, they have provided
orientation points for the development of drugs with antidepressant effects.
POSSIBLE REASONS OF SLOW PROGRESS IN THE YEARS THAT FOLLOWED

*Unavailability of psychotropic drugs with well-defined therapeutic effects, one of the essential prerequisites of successful neuropsychopharmacological research.

*The methodology of clinical investigations developed for the detection of drugs with a statistically significantly better chance to be effective in a particular diagnostic population than an inactive placebo and for the demonstration of their efficacy, is \textit{unsuitable} for the delineation of the therapeutic profile and identification of the treatment responsive subpopulations within the diagnostic groups.
Focused attention on the pharmacological heterogeneity in responsiveness to the new drugs within the diagnostic categories of classifications based on Kraepelin’s nosology, and called for a pharmacological re-evaluation of psychiatric diagnoses.
Diagnostic concepts based on Kraepelin’s nosology, such as schizophrenia and manic-depressive illness were split into several forms and sub-forms of disease.
Frank Fish
1964
opened up a perspective for progress by his findings of:

1. differential responsiveness in the six forms of disease diagnosed as schizophrenia in Kreapelinian classifications;

2. marked to moderate responsiveness to phenothiazine antipsychotics in 4 of 5 patients in 1 of the 6 forms: “affect-laden paraphrenia.”