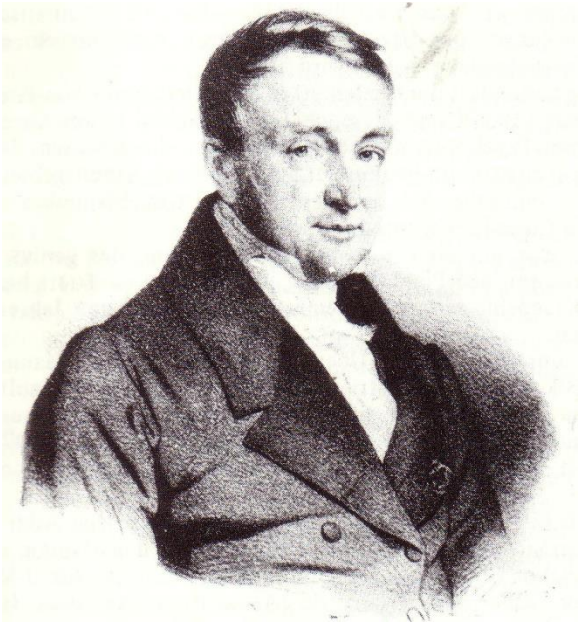


Jacques-Joseph Moreau de Tours
(1804-1884)

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.

SPECTROPHOTOFLUORIMETER (1957)

Capability to measure changes in the concentration of neurotransmitter monamines

NEUROPHARMACOLOGY
Studies the mode of action of centrally acting drugs

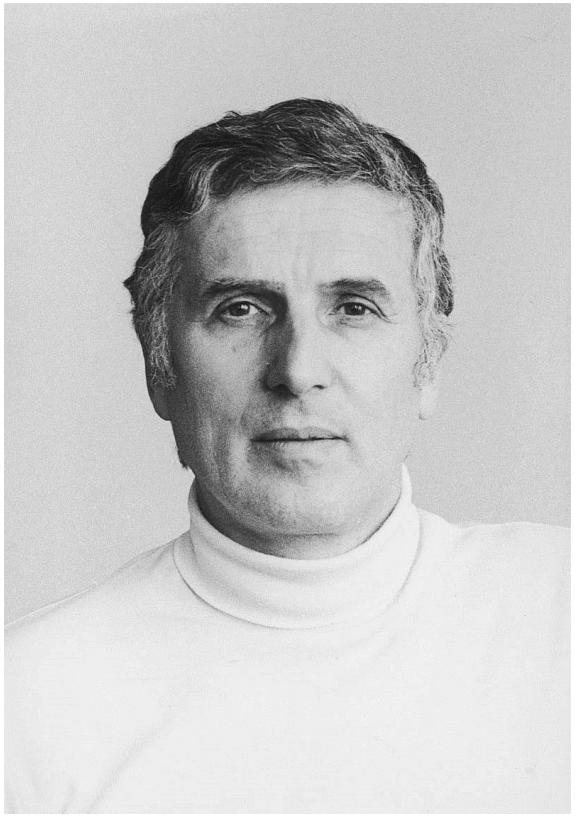
NEUROPSYCHOPHARMACOLOGY
Studies the relationship between neuronal and mental events with the use of centrally acting drugs

Abraham Wikler
The Relation of Psychiatry to Pharmacology
(1957)

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.

PROGESS IN NEUROPSYCHOPHARMACOLOGY

depends on a continuous dialogue between basic scientists and clinicians



Silvio Garattini

Organization of 1st international Symposium 1957

Ernst Rothlin

Founding president CINP1957 - 1960

Nathan Kline

Chairman 1st WPA symposium 1957

CHLORPROMAZINE

Development

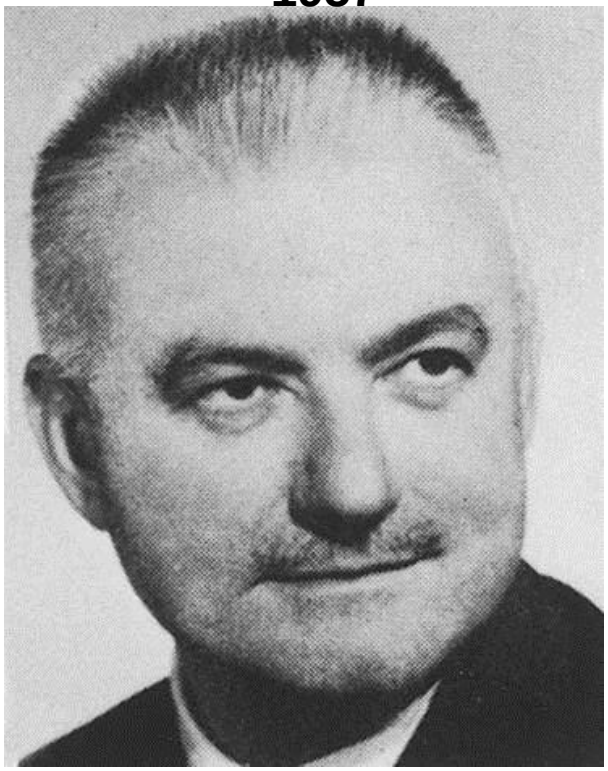
1937	**Bovet**	**synthesis of first antihistaminic drugs**
1949	**Laborit**	**potent sedating effect of promethazine**
1950	**Guiraud & David**	**promethazine controls agitation**
1951	**Charpentier et al**	**synthesis of CPZ (Dec.11)**
1952	**Laborit et al**	**recognition of potential use in psychiatry**
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)**

CHLORPROMAZINE

Albert Lasker Award
1957

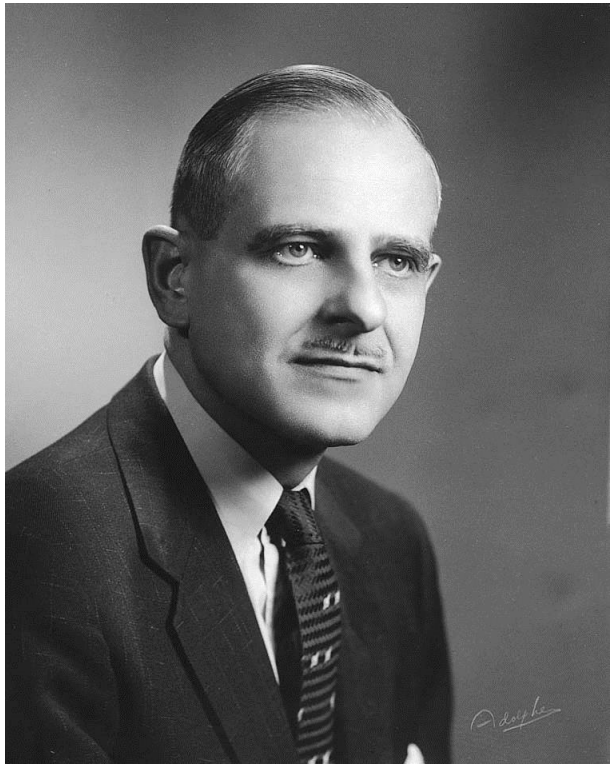
Henri Laborit

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)

1949	**Rustom Vakil**	**publication on antihypertensive effect**
1952	**(Rhone Poulenc**	**development & release of CPZ for clinical use)**
1952	**Mueller, Schlittler & Bein**	**isolation of reserpine from Rauwolfia root**
1953	**Hakim**	**Rauwolfia preparations in schizophrenia**
1954	**Delay et al**	**effective in mental disorders**
1954	**Kline**	**effective in mental disorders**
1954	**Noce,William & Rapoport**	**effective in mental disorders**
1954	**Weber**	**comparable to CPZ in action**
1954	**Steck**	**comparable to CPZ in producing EPS**
1954	**Freis**	**Reserpine may induce depression**
1955	**Mueller et al**	**Rauwolfia serpentina may induce depression**

RESERPINE

Albert Laskar Award

1957

Rustom Vakil

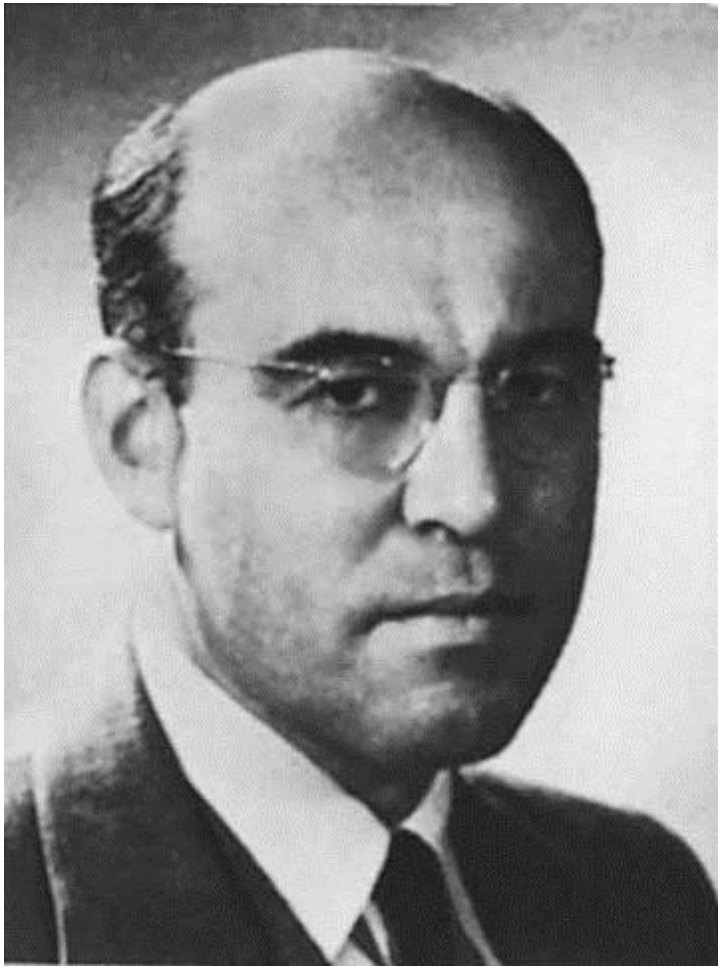
Producing a document that brought Rauwolfia alkaloids into Western medicine

Nathan Kline

Bringing to the attention the value of resperpine in the treatment of nervous and mental disorders

Robert Noce

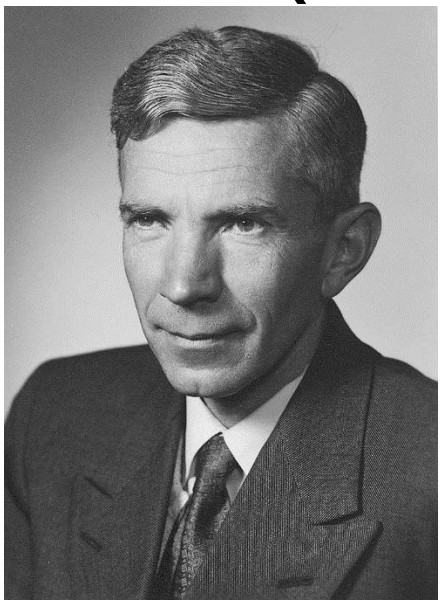
Recognizing the potential use of reserpine in the mentally defective



Henry Brill

After one-year large scale use of CPZ & reserpine Brill and Patton in 1957 reported a population fall in New York State Mental Hospitals

IMIPRAMINE (G22 355)



Roland Kuhn

1955 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

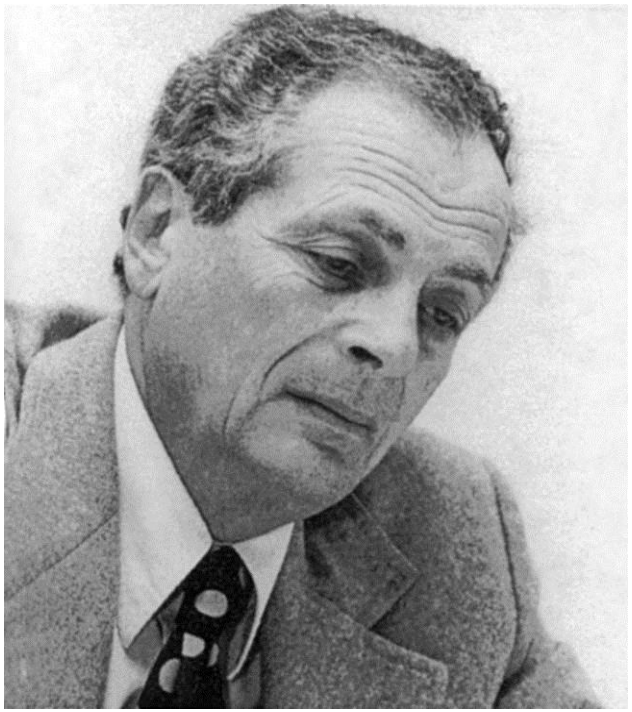
1957 (August 31) the first article on the antidepressant effect of the substance appears in the Swiss Medical Journal; (September 6) presents paper on the antidepressant effect of the substance (based on the treatment of 43 patients) at WPA congress; drug is released for clinical use in Switzerland with the generic name of imipramine and the trade name of Tofranil

IPRONIAZID & MONOAMINE OXIDASE

1937	**Blaschko**	**identification of MAO in tissues**
1937	**Pugh & Quastel**	**identification of MAO in brain**
1938	**Zeller**	**differentiation of MA, the enzyme responsible for the deamination of monoamines from DAO**
1951	**Herbert Fox**	**synthesis of iproniazid**
1952	**Selikoff et al.**	**iproniazid induces euphoria and overactivity in some tubercular patients**
1952	**Flaherty**	**iproniazid induced euphoria in a patient**
1952	**Zeller et al**	**iproniazid inhibits the activity of MAO**
1957	**Crane**	**iproniazid is an antidepressant**
1957	**Loomers et al.**	**iproniazid is an antidepressant**

INSTRUMENTAL TO THE DEVELOPMENT OF NEUROPHARMACOLOGY:

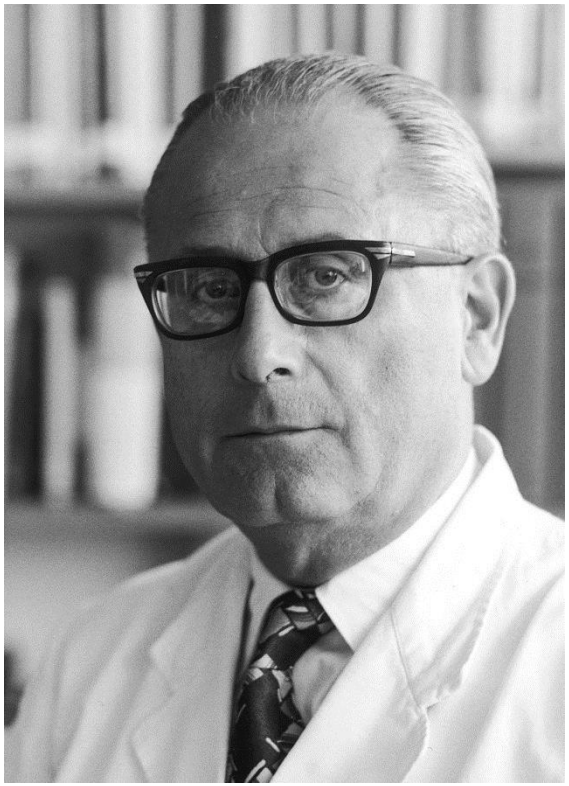
1953 Twarog & Page: demonstration of 5HT in the brain
1954 Vogt: demonstration of NE in the brain
1955 Bowman, Caulfield and Udenfriend: introduction of spectrophotofluorimeter



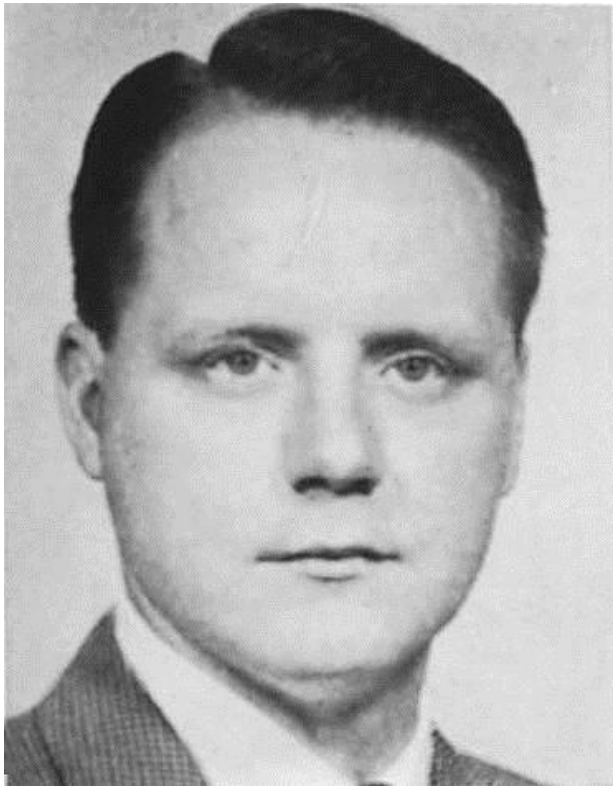
Sidney Udenfriend

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

WITHIN TWO-YEARS FROM THE TIME OF THE INTRODUCTION OF THE NEW TECHNOLOGY (1955 –1957) THE KEY EXPERIMENTS THAT WERE TO BECOME THE FOUNDATION OF NEUROPSYCHOPHARMACOLOGY WERE COMPLETED



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 bran 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 EPERIMENTS 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.

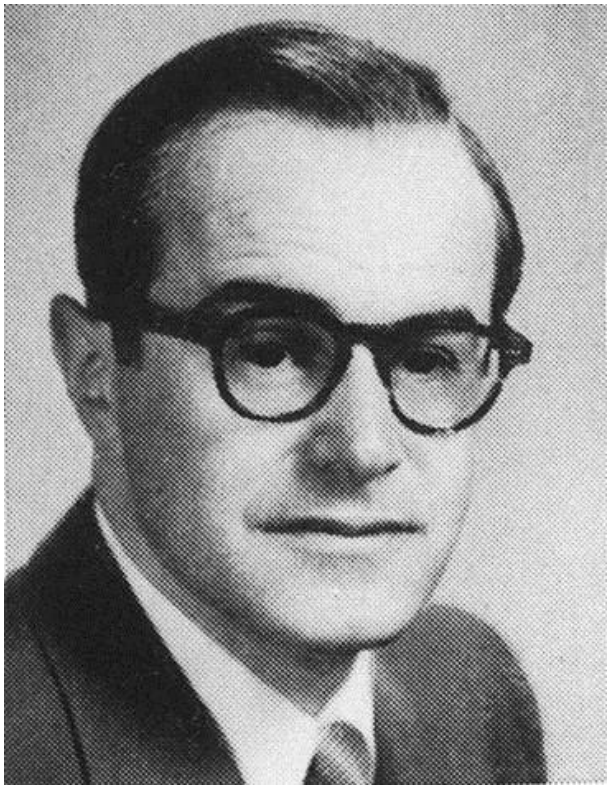
MONOAMINE DEPLETION AND MOOD DEPRESSANT EFFECT
Davies and Shepherd in 1955 reported that reserpine improved depression in their clinical trial.

However tenuous the relationships between elation and monoamine oxidase inhibition, and depression and monoamine depletion are, they have provided

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 pacebo and for the demonstration of their efficacy, is *unsuitable* for the delineation of the therapeutic profile and identification of the treatment responsive subpopulations within the diagnostic groups.**



Fritz Freyhan
1956-1959

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

Karl Leonhard
The Classification of Endogenous Psychoses (1957)

Diagnostic concepts based on Kraepelin's nosology, such as schizophrenia and 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.”