

Thomas A. Ban: Neuropsychopharmacology in Historical Perspective
Collated 28

**Profiles of clinicians and researchers who were instrumental for the birth
and/or contributed to the development of neuropsychopharmacology**

Edmundo Fischer, W. Horsley Gantt, Turan M. Itil, Hitoshi Itoh and
Paul Kielholz

CONTENTS

Edmundo Fischer by Edith Serfaty, August 1, 2013
W. Horsley Gantt by Thomas A. Ban, August 1, 2013
Turan M. Itil by Antonio Efifio Narfi August 1, 2014
Hitoshi Itoh by Hajime Kazamatsuri, November 20, 2014
Paul Kielhplz by Anyonio Egodio Nardi, October 9, 2014.

,

Edmundo Fischer by Edith Serfaty

Edmundo Fischer was born in Budapest in 1904 and received his M.D. in 1929 from the University of Pecs. He began his professional career as a neurologist and psychiatrist in his native country, but left Hungary in 1938, via Mexico and Chile, to settle in Argentina in 1950.

With the introduction of the first therapeutically effective psychotropic drugs in the treatment of mental illness, Fischer's interest turned to psychopharmacology and in 1960 he became founding director of the Laboratory of Experimental Psychiatry at Borda Hospital in Buenos Aires. Three years later, in 1963, he was instrumental in founding the Argentine Society of Psychopharmacology; and in 1965 he published *Psicofarmacologia*, co-authored by G. Poch and Ronaldo Ucha Udabe, one of the first textbooks in the field.

Stimulated by Fabing's observations in the mid-1950s on bufotenin's psychomimetic effects, Fischer became involved in measuring tryptamine metabolites in urine and reported on significantly higher urinary concentration of bufotenin-like substances in schizophrenia than in normal subjects. His findings fueled the ongoing controversy in the 1960s and early 1970s on the role of dimethylated psychotoxic tryptamine metabolites in the pathogenesis of schizophrenia.

Pursuing research with the employment of biochemical measures in different diagnostic groups of psychiatric patients, Fischer found decreased urinary elimination of phenylethylamine (PEA) in "endogenous depression." Subsequently, after demonstrating that PEA antagonized reserpine effects in pretreated rats, Fischer was among the first, in the early 1970s, to explore the possible use of phenylalanine, the precursor of PEA, in the treatment of depression.

In 1974 Fischer played a role in the founding the World Federation of Societies in Biological Psychiatry. He died in Buenos Aires one year later, in 1975, at age 71.

References:

Fischer E. Biogenic amines in schizophrenia. In: Hawkins D, Pauling L, editors. *Orthomolecular Psychiatry: Treatment of Schizophrenia*. San Francisco: W.H. Freeman, 1973, pp. 179-201.

Fischer E, Heller B, Nacchon M, Spatz H. Therapy of depression by phenylalanine. Preliminary note. *Arzneimittelforschung* 1975; 25:132.

Fischer E, Heller B, Miro AH. β -Phenylethylamine in human urine. *Arzneimittelforschung* 1968; 18:1486.

Fischer E, Lagrevere TA, Vazquez AJ, Di Stefano AO. Bufoteninlike substance in the urine of schizophrenics. *J Nerv Ment Dis* 1961; 133:441-7.

Fischer E, Patz H. Studies on urinary elimination of bufotenin-like substances. *Biological Psychiatry* 1970; 2:235-40.

Fischer E, Poch G, Ucha Udabe R. *Psicofarmacologia*. Buenos Aires: Lopez Egocheyen; 1965.

Fischer E, Spatz H, Fledel T. Bufotenin-like substances in form of glucuronide in schizophrenic and normal urine. *Psychosomatics* 1971; 12:278-80.

Fischer E, Spatz H, Heller B, Reggiani H. Phenethylamine content of human urine and rat brain, its alterations in pathological conditions and after drug administration. *Experientia* 1972; 15:307-8.

Saavedra.J, Fischer E. Antagonism of β -phenethylamine derivatives and serotonin blocking drugs upon serotonin, tryptamine and reserpine behavioral depression in mice. *Arzneimittelforschung* 1970; 20:952-7.

August 1, 2013

W. Horsley Gantt by Thomas A. Ban

Horsley Gantt was born in 1893 in Wingina, Virginia and received his M.D. in 1920 from the University of Virginia at Charlottesville. Gantt began with his professional career at the University of Maryland in Baltimore studying “liver pathology,” but his interest shifted after serving for a year, from 1922 to 1923, as Medical Chief of the Petrograd (now Saint Petersburg) Unit of the American Relief Administration in Russia, at the time the Union of Soviet Socialist Republics.



In 1924 Gantt joined Ivan Petrovich Pavlov and for five years he conducted research in conditioning at his Institute of Experimental Medicine. After returning to the United States he continued his research in conditioning from 1930 to 1958, as Director of the Pavlovian Laboratory, The Johns Hopkins University School of Medicine and, subsequently, from 1959 to 1980, as Senior Scientist in the Pavlovian Research Laboratory of the Veterans Administration Hospital, at Perry Point, Maryland. He conducted his research primarily in animals, but also in man, including patients with mental pathology. He held appointments during the corresponding periods in the departments of psychiatry at Johns Hopkins and at the University of Baltimore.

Gantt began his research in psychopharmacology in the mid-1930s. Over a period of 40 years he was involved, first in studying “drug effects on conditional and unconditional reflexes” in general, then in studying the differential effects of drugs on “autonomic and somatic conditioned reflexes” and ultimately in the study of “conditioning of drug effects.” His findings with alcohol, acetylcholine, adrenaline, amphetamine, caffeine, chlorpromazine and reserpine, in the first set of studies, were supportive of Pavlov and his associates’ reports that drug effects were dependent on the “temperamental type” of animals. In the course of these studies he showed that acetylcholine improved conditional reflexes more in “neurotic” than in “normal” dogs, whereas adrenaline was less disruptive in “normal” than in “neurotic” animals. In the second set of studies Gantt and his associates revealed that some drugs, for example chlorpromazine, reserpine and 5-hydroxytryptophan, influenced motor and cardiac conditional reflexes to the same degree, whereas others, for example mescaline, meprobamate and metrazol, affected autonomic conditional

reflexes preferentially, and others again, for example, morphine, had a preferential effect on motor conditional reflexes. Finally, in the third set of studies, Gantt and his associates demonstrated that there was conditioning only to the central effect, but not to the peripheral effect of drugs. Thus, cardiac conditional reflexes could be formed to the central effect of bulbocapnin, but not to the peripheral effect of acetylcholine.

Gantt's studies stimulated interest in "Pavlovian" research, leading to the founding of the Pavlovian Society of North America in 1955 and to the Collegium Internationale Activitatis Nervosae Superioris about 10 years later. Gantt was founding President in both of these societies.

Horsley Gantt died, in 1980, at age 83.

References:

Bridger WH, Gantt WH. Effect of mescaline on differentiated conditional reflexes. *Am J Psychiatry* 1956; 113:352-60.

Freile M, Gantt WH. Effect of adrenaline on excitation, inhibition and neuroses. *Trans Am Neurol Assoc* 1944; 70:180-1.

Gantt WH. Effect of alcohol on cortical and subcortical activity measured by the conditional reflex method. *Bull Johns Hopkins Hosp* 1935; 56:61-83.

Gantt WH. Psychopharmacology and conditional reflexes. *Cond Reflex* 1970; 5:109-18.

Perez-Cruet J, Gantt WH. Conditional reflex electrocardiogram of bulbocapnine. Conditioning of the T wave. *Am Heart J* 1964; 67:61-72.

Stoff DH, Bridger WH. Horsley Gantt, the first American psychopharmacologist. In: McGuigna FJ, Ban TA, editors. *Critical Issues in Psychology, Psychiatry and Physiology. A Memorial to W. Horsley Gantt*. New York: Gordon and Breach Science Publishers; 1987, pp. 177-87.

August 1, 2013

Turan M. Itil by Antonio Egidio Nardi

Turan Itil was born in Bursa, Turkey, in August 12, 1924. He received his MD from the Medical College, University of Istanbul, in 1948 and completed his training in neurology and psychiatry in the early 1950s at the University of Tübingen in Germany. Subsequently, he joined Fritz Flügel's Department of Neuropsychiatry in Erlangen, Germany (Itil 1998, 2011).

Itil became involved in studying clinical and electroencephalographic changes with centrally acting drugs in collaboration with Dieter Bente in the mid-1950s. It was in the course of their first study, in which they tested the therapeutic effect of promethazine on phantom pain, that he learned that drugs which affect human behavior also produce effects on the human electroencephalogram (EEG) (Bente and Itil 1954; Itil 1998). Pursuing further the same line of research, they reported on the clinical and electroencephalographic effects of chlorpromazine in 1954 and of reserpine, methamphetamine and lysergic acid diethylamide in 1957 (Bente and Itil 1954, 1957a,b). In 1957, at the First CIMP Congress in Rome, Bente and Itil (1959) reported on the differences in chlorpromazine-induced and natural sleep; and in 1960, at the Second CIMP Congress in Basel, Antonio Egidio Nardime, Flügel, Bente, Itil and Molitoris reported their findings with acylated piperazine phenothiazines that was allegedly instrumental in the clinical development of butaperazine (Bente and Itil 1959; Flügel, Bente, Itil and Molitoris 1961). It was also in 1961 that Itil published first on the differential effects of neuroleptics and thymoleptics on the EEG.

In 1963 Itil joined Max Fink at the Missouri Institute of Psychiatry where they developed a digital computer analysis of the human EEG that they referred to as quantitative EEG, or pharmaco-EEG (Fink, Itil and Shapiro 1967); and he set up a laboratory for the screening, early clinical evaluation and monitoring psychotropic effects (Fink, Shapiro, Hickman and Itil 1968; Itil 1966, 1968; Itil, Shapiro and Fink 1968). It was in this laboratory in the mid-1960s that he found that the pentothal-induced change in the EEG could be used as a prognostic index in drug therapy of psychotic patients (Itil 1965); and demonstrated, in collaboration with Samuel Gershon and Max Fink that tetrahydroamino acridine could reverse not only the delirium, but also the EEG changes associated with delirium induced by anticholinergic drugs (Itil 1966; Itil and Fink 1966). It was also in this laboratory, in collaboration with Polvin and Hsu, that he revealed that Org GB 94 (mianserin), a tetracyclic substance, has antidepressant properties (Itil, Polvin and Hsu 1972). In

1974 Itil moved from the University of Missouri to the New York Medical College and established, in Terrytown, HZI Research Center Laboratory for using pharmaco-EEG in the identification of psychoactive properties of drugs and in the prediction of their therapeutic activity, i.e., whether they had characteristics of antipsychotics, antidepressants, cognitive enhancers or anxiolytics (Itil 1972). Among the early drugs studied at the center were lisuride, an antiparkinson drug related to dopaminergic ergoline compounds, and mestrolone, a synthetic androgen preparation (Itil, Herrmann and Akpinar 1978a; Itil, Herrmann, Blasucci and Freedman 1978b); and among the last was ginkgo biloba, a plant extract with central nervous system effects, he reported on in 1996 (Itil, Eralp, Tsambis, Itil and Stein 1996).

In the late 1990s, Itil moved back to Turkey and died in Mersin, Turkey, April 29, 2014, at age 89.

References:

- Bente D, Itil TM. Periphere Anästhesie und Schmerzgeschehen. *Acta Neuroveg* 1954; 7:258-62.
- Bente D. Itil M. Zu Wirkung des Phenothiazin Körpern Megaphen auf das menschliche Hirnströmbild. *Arzneimittel Forschung* 1954; 4:418-23.
- Bente D, Itil T. Elektroenzephalographische Veränderungen unter extreme hohe Reserpin dosen. In: Garattini S, Ghetti V, editors. *Psychotropic Drugs*. Amsterdam: Elsevier; 1957a, pp. 294-6.
- Bente D, Itil TM. Vergleichende klinischelektonzephalograpische Untersuchungen mit Pervitin und LSD 25. In: Garattini S, Ghetti V, editors. *Psychotropic Drugs*. Amsterdam: Elsevier; 1957b, pp. 284-5.
- Bente D, Itil M. A comparison of the action of various phenothiazine compounds on the human EEG. In: Bradley PB, Deniker P, Radouco-Thomas C, editors. *Neuropsychopharmacology*. Amsterdam: Elsevier; 1959, pp.456-8.
- Fink M, Itil TM, Shapiro DM. Digital computer analysis of the human EEG in psychiatric research. *Compr Psychiatry* 1967; 8:521-38.
- Fink M, Shapiro D, Hickman C, Itil T. Quantitative analysis of the electroencephalogram by digital computer methods. III: Applications to psychopharmacology. In: Kline NS, Laska E, editors. *Computers and Electronic Devices in Psychiatry*. New York: Grune & Stratton; 1968, pp. 108–23.
- Flügel F, Bente D, Itil TM, Molitoris B. Klinische und elektroenzephalographische

Untersuchungen in der Reihe der acylierten Piperazin-Phenothiazin Derivate. In: Rothlin E, editor. Neuro-Psychopharmacology. Volume 2. Amsterdam: Elsevier; 1961, pp. 236-43.

Itil M. Elektroenzephalographische Befunde zur Klassifikation neuro - und thymoleptischer Medikamente. Med Exp 1961; 5:347-63.

Itil TM. Pentothal-induced changes in EEG as a prognostic index in drug therapy of psychotic patients. American Journal of Psychiatry 1965; 121:996-1002.

Itil TM. Quantitative EEG changes induced by anticholinergic drugs and their behavioral correlates in man. In: Wortis J, editor: Recent Advances in Biological Psychiatry. Volume 8. New York: Plenum Press; 1966, pp. 151-73.

Itil, TM. Electroencephalography and pharmacopsychiatry. In: Freyhan F, Petrilowitsch N, Pichot P, editors. Modern Problems of Pharmacopsychiatry vol 1. Basel: Karger; 1968, pp. 163-94.

Itil TM. Quantitative pharmaco-electroencephalography in the discovery of a new group of psychotropic drugs. Diseases of the Nervous System 1972; 338:557-9.

Itil TM. First use of placebo. In: BanTA, Healy D, Shorter E, editors. The Rise of Psychopharmacology and the Storof CINP. Budapest: Animula; 1998, p. 157-60.

Itil TM, interviewed by Andrea Tone. In: Ban TA, editor. An Oral History of Neuropsychopharmacology. (Volume 2: Neurophysiology, editor Max Fink). Brentwood: American College of Neuropsychopharmacology; 2011, pp.35-45.

Itil TM, Eralp E, Tsambis E, Itil KZ, Stein U. Central nervous system effects of ginkgo biloba, a plant extract. American Journal of Therapeutics 1996; 1:63-73.

Itil TM, Fink M. Anticholinergic drug-induced delirium: experimental modification, quantitative EEG and behavioral correlations. Journal of Nervous and Mental Diseases 1966; 143:492-507.

Itil TM, Herrmann WM, Akpınar S. Prediction of psychotropic properties of lisuride hydrogen maleate by quantitative pharmaco-electroencephalography. Internat Journal of Clinical Psychiatry 1975; 12:221-233.

Itil TM, Polvan N, Hsu W. Clinical and EEG effects of GB-94, a "tetracyclic" antidepressant (EEG model in discovery of a new psychotropic drug). Current Therapeutic Research 1972; 14: 395-413.

Itil TM, Shapiro DM, Fink M. Differentiation of psychotropic drugs by quantitative EEG analysis. Agressologie 1968; 9:267-280.

August 21, 2014

Hitoshi Itoh by Hajime Kazamatsuri

Hitoshi Itoh was born in Yokohama, Japan, on September 21, 1925. He received his medical degree from the Ciba University School of Medicine in 1950. After graduation from medical school he spent five years at the Institute of Infectious Disease Research, Tokyo University, and worked for about five years in immunology and neurochemistry. Subsequently, he began with his training in psychiatry at the Keio University Hospital in Tokyo in 1955.

Itoh was appointed associate professor of psychiatry at the Keio University School of Medicine in 1973 and became Director of the Psychopharmacology Research Group. He translated many European and American books related to neuropsychopharmacology into Japanese and wrote many papers on topics related to the field (Itoh 1981; Itoh, Ichimaru, Kawakita et al. 1971; Itoh, Miura, Yagi et al. 1977; Itoh, Ohtsuka, Ogita et al. 1977; Itoh, Yagi, Fujii et al. 1984). He also edited several books on psychotropic drugs (Itoh and Miura 1973).

Itoh was councilor of the CINP from 1984-1988. He is regarded as one of the pioneers of clinical psychopharmacology in Japan.

Itoh died on April 30, 1985, at the age of 60.

References:

Itoh H. Drug-induced tardive dyskinesia. In: Essman WB, Valzelli L, editors. *Current Development in Psychopharmacology*. Volume 6. Amsterdam: Springer; 1981, pp 93-126.

Itoh H, Ichimaru S, Kawakita Y, Kudo Y, Kurihara M, Satoh Y, Takahashi R. A Clinical study for the evaluation of anxiolytic drugs. In: *Advances in Neuro-Psychopharmacology*, Vinar O, Votava S, Bradley, editors. North-Holland Publ. Comp., Amsterdam, 1971, pp 225-35.

Itoh H, Miura S, editors. *Psychotropic Drugs - Efficacy and Side Effects*. Tokyo: Igaku-Tosho-Shuppan; 1973.

Itoh H, Miura S, Yagi G, Sakurai S, Ohtsuka N. Some methodological considerations for the clinical evaluation of neuroleptics-comparative effects of clozapine and haloperidol on schizophrenics. *Folia Psychiatrica et Neurologica Japonica* 1977a; 31(1):17-24.

Itoh H, Ohtsuka N, Ogita K, Yagi G, Miura S, Koga Y. Malignant neuroleptic syndrome – its present status in Japan and clinical problems. *Folia Psychiatrica et Neurologica Japonica* 1977b;

31(4):559-76.

Itoh H, Yagi G, Fujii Y, Iwamura K, Ichikawa K. The relationship between haloperidol blood levels and clinical responses. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 1984; 8(2):285-92.

November 20, 2014

Paul Kielholz by Antonio Egidio Nardi

Paul Kielholz was born November 15, 1916, in Brugg, Switzerland, and received his MD in 1943 from the Faculty of Medicine, University of Zurich. In 1947 Kielholz joined John Eugen Staehelin's Department of Psychiatry at the University of Basel and 12 years later, in 1959, succeeded Staehelin as head of the Department and Director of the University Clinic. He remained in the same position until his retirement in 1985.

Kielholz began his research in the late 1940s by exploring the use of narcosis and muscle relaxants in electroconvulsive therapy (ECT) (Heuscher and Kielholz 1949; Kielholz and Heuscher 1949) and of the "perfusion method" in the treatment of "acute catatonia" (Kielholz 1949). In the early 1950s he extended his research to the study of "chronic morphinism" (Kielholz 1952). Then, in 1953, he co-authored with Staehelin the first paper on the therapeutic effect of chlorpromazine (CPZ) published outside of France (Staehelin and Kielholz 1953). Pursuing his research further with CPZ, in 1954 he reported on the therapeutic effects of the substance in depression, mania and drug (morphine and barbiturate) withdrawal (Kielholz 1954). The turning point in Kielholz's research was the publication of his report in 1958, with Raymond Battegay, in which they provided further substantiation of Roland Kuhn's (1957) discovery of the therapeutic effect of imipramine (IMI) in some depressed patients (Kielholz and Battegay 1958). Subsequently, he was a member of the team which, in 1961, recognized that desmethylimipramine (DMI) was an active metabolite of IMI and implicated the major role of DMI in IMI's antidepressant effect (Brodie, Dick, Kielholz, et al. 1961). In the early 1970s Kielholz was chairman of two influential symposia ("Depressive Illness" and "Masked Depression") which were instrumental in establishing the place of pharmacotherapy in the treatment of depression (Kielholz 1972, 1973). By the late 1970s there were several drugs available for the treatment of depression and in 1979 Kielholz was among the first to relate the pharmacological activity of these drugs to their therapeutic profile (Kielholz 1979). During the 1970s Kielholz was also involved in studying the effects of "pharmacotherapy of toxicomania" (Kielholz 1974); the effects of alcohol and other drugs on "driving behavior" (Kielholz and Hobl 1977); and in developing treatment strategies, e.g., intravenous administration of antidepressants, for therapy refractory depression (Kielholz, Terzani and Gastpar 1979). Exploring possible treatments for therapy of refractory depression dominated Kielholz's research during the 1980s (Kielholz 1986, 1990; Kielholz, Terzani, Gastpar et al. 1982).

Paul Kielholz died on May 25, 1990. He was 73 years old.

References:

Brodie B, Dick P, Kielholz P, Poeldinger W, Theobald W. Preliminary pharmacological and clinical results with desmethylimipramine (DMI), G35020, a metabolite of imipramine. *Psychopharmacologia* 1961; 19:457-74.

Heuscher J, Kielholz P. Praktischerfahrungen und Experimentelleuntersuchungenbei Modifizierten Elektroschock Behandlungen. *Schweizerische Medizinische Wochenschrift* 1949; 70:853-6.

Kielholz P. ÜberErgebnisse der Behandlung Acuter Katatonienmit der Durchblutungsmethode. *Schweizer Archiv für Neurologie und Psychiatrie* 1949; 63:23-45.

Kielholz P. Behandlung und Prognose des Chronischen Morphinismus.Schweizerische Medizinische Wochenschrift 1952; 82:1325-9.

Kielholz P. ÜberdieLargactilwirkungbeidepressivenZuständen und Maniensoviebei der Entziehung von Morphin-und Barbitursüchtigen. *Schweizer Archivfür Neurologie und Psychiatrie*1954; 73:291-309.

Kielholz P. Depressive Illness, Diagnosis, Assessment, Treatment. Kiehlolz P, editor. Born/Stuttgart/Vienna: Hans Huber Publishers; 1972.

Kielholz P. Masked Depression. Kielholz P, editor. Born/Stuttgart/Vienna: Hans Huber Publishers; 1973.

Kielholz P. Classification of depression and the activity profile of antidepressants. *Progress in Neuro-psychopharmacology and Biological Psychiatry* 1979; 3:59-63.

Kielholz P. Treatment of therapy-resistant depression. *Psychopathology* 1986; 19:194-200.

Kielholz P. Treatment of therapy refractory depressions with intravenous infusions of antidepressants. (Title translated into English from the Russian original.) *Zhurnal Nevropatologii PsikhiiatriiImeni* 1990; 90:53-6.

Kielholz P, Battegay R. Behandlung depressive ZustandsbilderunterspeziellerBerücksichtigung von Tofranil, einem Neuen Antidepressivum.Schweizerische Medizinische Wochenschrift 1958; 763-7.

Kielholz P, Heuscher J. Elektroschock-therapien Narkosemit curarebehandlung. *Schweizerische*

Medizinische Wochenschrift 199; 9:592-6.

Kielholz P, Hobi V. Alkohol und Fahrverhalten. Therapeutische Umschau 1977; 34:803-13.

Kielholz P, Terzani S, Gastpar M. Treatment of therapy resistant depression. International Pharmacopsychiatry 1979; 14:94-100.

Kielholz P, Terzani S, Gastpar M, Adams C. Zur Behandlung therapieresistenter Depressionen. Ergebnisse einer kombinierten Infusionstherapie. Schweizerische Medizinische Wochenschrift 1982; 112:1090-5.

Kuhn R. Über die Behandlung depressiver Zustände mit einem Minodibezylderivat (G 22. 355). Schweizerische Medizinische Wochenschrift 1957; 87:1135-40.

Stachelin J, Kielholz P. Largactil, ein neues vegetatives Dämpfungsmittel bei psychischen Störungen. Schweizerische Medizinische Wochenschrift 1953; 83:581-6.

October 9, 2014

April 23, 2020