Phenothiazines and Structurally Related Drugs:

Basic and Clinical Studies

Editors:
Earl Usdin, Helmut Eckert, and Irene S. Forrest

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PHENOTHIAZINES AND STRUCTURALLY RELATED DRUGS: BASIC AND CLINICAL STUDIES

Proceedings of the 4th International Symposium on Phenothiazines and Related Drugs, held in Zurich, Switzerland, September 9-13, 1979

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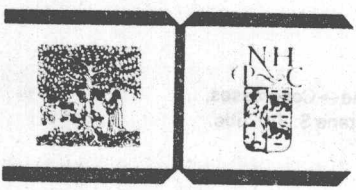

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Dedication

Although there is some controversy as to who is the father--or, to avoid charges of sexism, the parent--of clinical phenothiazine-ology, there is little question as to who is the parent of laboratory phenothiazine-ology: Irene S. Forrest. In hospitals and laboratories throughout the world, whenever there is a question of patient compliance with regard to ingestion of a phenothiazine, the almost universal procedure is to request a "Forrest's test" on the patient's urine. When there is a discussion of the number of metabolites of chlorpromazine, the standard reply is that Irene Forrest has indicated that there are 168 (even though this ignores the fact that Dr. Forrest has been demonstrating more and more chlorpromazine metabolites in recent years).

Besides Irene's preeminence in the field, and her dedicated work on each of the international symposia on phenothiazines and structurally-related drugs (certainly the last several meetings would never have taken place without her efforts), it is appropriate to dedicate this particular volume to Dr. Forrest since she has recently "retired". If you were to visit her lab you would have difficulty in understanding the use of the term "retired" since she still puts in a full day in the laboratory, since she still directs the same dedicated group, since she still reads, writes, referees, talks, advises. Irene's signs of retirement are subtle: she no longer gets to the lab every day before 8:00 a.m., she now receives retirement pay rather than salary; this last is probably the crux of present-day retirement.

It is with gratitude and thanks that the Organizing Committee of the Fourth International Symposium on Phenothiazines and Related Drugs dedicate this volume to a pioneer in the field of phenothiazine research, to one who is, without question, the most active "retired worker" in the field, Dr. Irene S. Forrest.

Preface

It was a great pleasure and honor to welcome the participants to our Fourth International Symposium on Phenothiazines and Structurally Related Drugs. It was gratifying to see many familiar faces; sad to miss some of the old-timers whose presence at our conferences we took for granted; and encouraging to see many new and young people.

For those who are unfamiliar with our periodic Symposia, we should like to mention that we started our international get-togethers in Paris (1962 and 1967); the third one was held at the National Institute of Mental Health in Rockville, Maryland (1973). Each of our conferences was structured to reflect the state of the art. We like to think that the Proceedings of each of our meetings were useful and provided information to the research workers in all concerned disciplines for many years.

When we first convened in 1962, the clinical know-how was quite advanced. Chlorpromazine had been around for 10 years; had been used therapeutically for almost that long in Europe and Canada; and for a few years less in the United States. Laboratory investigation and development of suitable methodology for the assay of chlorpromazine, its many metabolites, and the new structurally-related drugs that had been introduced rapidly after the success of chlorpromazine, were in their infancy and far from satisfactory. However, some of the basic aspects of the chemistry of the substituted phenothiazines, particularly the facile formation of free radical derivatives, appeared of interest to the early conferees, clinical as well as basic scientists. We encouraged the clinicians to exchange views with the basic scientists. For the basic scientists, this is imperative: Unless they can design their studies to provide new knowledge on the mode of action of the psychoactive drugs or to provide solid data on what constitutes therapeutic blood concentrations for the various neuroleptics and antidepressants, the cooperation between clinicians and biochemists will remain naught but a pious wish. Closer cooperation between clinicians and basic scientists, as it exists presently in only very few hospitals, would be tremendously useful for both partners. Thus, good clinical observations by the clinical team could provide reliable information on responders and non-responders in a given drug study. With this information the biochemists could go to work and determine not only blood-drug concentrations, but they could also evaluate patterns of drug metabolism and relative abundances of individual drug metabolites. Some initial work along these lines has indeed been done, but neither for the metabolites of chlorpromazine nor for those of thioridazine or mesoridazine has the body of data obtained been broad enough to allow sweeping conclusions or valid generalizations to be drawn.

If psychopharmacology is to claim its rightful place not only in active treatment centers such as mental hospitals, but also in academic psychiatry, the biologically-minded psychiatrists should collaborate closely with their basic science colleagues.

There is still, at present, an unmistakable tendency in many university departments of psychiatry in the USA to teach their students, interns, and residents according to the gospels of Freud, Jung, Adler, Sullivan, etc., leaving psychopharmacology to a few haphazard lectures and seminars. Residents in teaching hospitals will often be exposed only to the latest drug trials of investigational drugs and will generally learn almost nothing about the revolution in the treatment of mental patients in the 1950's and 1960's. The 1970's have brought few advances and, in some places, obvious deterioration of treatment, with heavy reliance on encounter and group therapies and other forms of social psychiatry rituals. While these may be appropriate for certain personality disorders, the genuinely psychotic patient is not likely to be optimally rehabilitated by talking. If we do not want to commit to oblivion the dedicated work of Laborit, Delay and Deniker, their pioneer colleagues Kielholz and Labhardt in Switzerland, and other early psychopharmacological clinicians, we had better provide sound scientific bases for the clinicians who most of the time have to rely on their clinical intuition--an art, rather than hard scientific facts--to select the drug of choice, the dose, the mode of administration, for each individual patient.

One of the reasons the 1970's have seen such a decline in effective pharmacology of mental patients is the physicians' reluctance to use adequate doses of the neuroleptics--all of which may produce side effects, especially in long-term continuous therapy. In our part of the world, a psychiatrist can--and, occasionally is--sued for malpractice if a patient develops tardive dyskinesia. Although in well-run wards the incidence of this type of movement disorder may not exceed 5% of the patient population, the prevention and treatment of this side effect must be a prime goal of research in psychopharmacology.

We should like to thank Sandoz, our gracious hosts, for making this symposium possible and we are also grateful to our co-sponsors Boehringer (Ridgefield, Connecticut), Ciba-Geigy (Basel, Switzerland), Smith Kline & French (Wellwyn Garden City, U. K.), Squibb (Zurich, Switzerland) and Von Heyden (Munich, Germany) for helping to defray travel costs of some of the participants.

Irene S. Forrest

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Abbreviations

ACH = acetylcholine
ADP = adenosine diphosphate
AIMS = A.I.M.S. = Abnormal Involuntary Movement Scale
AMI = amitriptyline
AMP = adenosine monophosphate
AMPH = amphetamine
ANOVA = analysis of variance
AOAA = aminooxyacetic acid
AT = amitriptyline
ATP = adenosine triphosphate
ATPase = adenosine triphosphatase
AUC = area under the curve

BLM = bucco-linguo-masticatory syndrome
BPRS = Brief Psychiatric Rating Scale
BSA = bovine serum albumin

cAMP = cyclic AMP
CAR = conditioned avoidance reflex
CAS = central adrenergic system
CBC = complete blood count
CDR = calmodulin
CGI = Clinical Global Inventory
CI = chemical ionization
CLO = clopenthixol
CLZ = clozapine
CNS = central nervous system
CPRS = Comprehensive Psychopathological Rating Scale
CPT = chlorprothixene
CPZ = chlorpromazine
CPZe = CPZ equivalents
CS = corpus striatum
CSF = cerebrospinal fluid

DA = dopamine
DH = diethazine HCl
DHA = dihydroalprenolol
DMI = desmethylimipramine
DNAase = deoxyribonuclease
DOPAC = 3,4-dihydroxyphenylacetic acid

E = extraction fraction
ECT = electroconvulsive (shock) therapy
EDTA = ethylenediaminetetraacetic acid
EKG = electrocardiograph
EPS = extrapyramidal symptoms

FC = frontal cortex
FLU = flupenthixol
FPH = fluphenazine HCl
FPZ = fluphenazine

GABA = γ-aminobutyric acid
GAD = glutamic acid decarboxylase
GAG = γ-acetylenic GABA
GC = gas (liquid) chromatography
GC/MS = gas chromatography/mass spectroscopy
GLC = gas liquid chromatography
α_1-GP = α_1-acid glycoprotein

HAL = haloperidol
HDL = high density lipids
5-HIAA = 5-hydroxyindole acetic acid
HPLC = high pressure (or, performance) liquid chromatography
HSA = human serum albumin
5-HT = serotonin
HVA = homovanillic acid
HYP = hypothalamus

IMI = imipramine

L.A.N. = long-acting neuroleptics
LDL = low density lipids
LEVO = levomepromazine
LH = luteinizing hormone
LHRH = LH releasing hormone
L.S.D. = least significant difference

MAO = monoamine oxidase
MESO = mesoridazine
MOPEG-SO_4 = 3-methoxy-4-hydroxyphenylethylene glycol sulfate
MRC = (UK) Medical Research Council
MS = mass spectroscopy

NA = noradrenaline
NAD = nicotinamide adenine dinucleotide
NADH = reduced NAD
NAOT = nucleus accumbens-olfactory tubercle
NE = norepinephrine
NEM = N-ethyl maleimide
NHDA = National Hereditary Disease Assoc.
NIAMDD = National Institute of Arthritis, Metabolic and Digestive Diseases
NIMH = National Institute of Mental Health
NMR = N.M.R. = nuclear magnetic resonance
NOSIE = Nurses' Observation Scale for In-patient Evaluation
NRS = Nurses' Rating Scale
NT = nortriptyline
N.Y.U. = New York University

6-OHDOPA = 6-hydroxydopamine

PBS = phosphate-buffered saline
PCPM = prochlorperazine maleate
PD = phenothiazine derivatives
PEA = β-phenethylamine

PER = PERA = perazine
PERI = pericyazine
PH = promethazine HCl
PHP = photo-product
PMH = promazine HCl
PPZ = perphenazine
PRL = prolactin

RDC = Research Diagnostic Criteria
RIA = radioimmuno assay
RNAase = ribonuclease
R-SO = ring sulfoxides
RT = retention time

SAR = structure-activity relationships
SDS = sodium dodecyl sulfate
SDZ = sulforidazine
SEE = standard error of estimate
SIM = selected ion monitoring
SIR = stable isotope
SMA = spontaneous motor activity
SPI = spiperone

TAT = tyrosine aminotransferase
TCA = trichloracetic acid, or, tricyclic antidepressant
TD = tardive dyskinesia
TDZ = thioridazine
THIO = thioridazine
TLC = thin layer chromatography
TMB = Tris maleate buffer
TPH = triflupromazine HCl
TRH = thyrotropin releasing hormone
t-RNA = transfer RNA
TSH = thyrotropin

VLDL = very low density lipids

WPIC = Western Psychiatric Institute & Clinic (Univ. of Pittsburgh)

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