Drug and Alcohol Dependence, 23 (1989) 183–218
Elsevier Scientific Publishers Ireland Ltd.

The Committee on Problems of Drug Dependence: A legacy of the National Academy of Sciences. A historical account

Everette L. May[a] and Arthur E. Jacobson[b]

[a]*Department of Pharmacology and Toxicology, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA 23298-0613 and* [b]*Laboratory of Medicinal Chemistry, National Institute of Diabetes, Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD 20892 (U.S.A.)*

(Received March 20th, 1989)

The history of The Committee on Problems of Drug Dependence is traced from its beginning (1929) as The Committee on Drug Addiction to 1989, its sixtieth anniversary. A brief account of the etiology of The Committee from The Bureau of Social Hygiene, established in New York City by John D. Rockefeller, Jr. in 1913 is also given.

Key words: physical dependence potential; abuse liability; narcotic analgesics and antagonists; agonist/antagonists; stimulants and depressants; animal and human testing; drug addiction and evaluation.

Introduction

The purpose of this article is to review the history of the Committee on Problems of Drug Dependence (CPDD). This history was undertaken on the recommendation of CPDD, acting on the suggestion of its Chairman, Dr. Mary Jeanne Kreek, in order to summarize and then update the detailed history presented in the volume 'The National Research Council Involvement in the Opiate Problem (1928–1971) by Nathan B. Eddy, published by The National Academy of Sciences [1]. Of particular concern and interest are the years that followed the termination of sponsorship by The National Research Council in 1976 and the transition years that culminated in the structuring of an incorporated committee affiliated with several highly regarded scientific societies. The authors have been closely associated with Committee activities since 1960 (E.L.M.) and 1974 (A.E.J.), principally as coordinators of the testing program for evaluating the physical dependence potential and abuse liability of analgesics and other compounds, and as members of the Board of Directors and Executive Committee. It is hoped that the achievements of the CPDD since its inception (1929) will be well focused and that this history will give insights into contributions of CPDD to solutions of drug-dependence problems. Although the principal source of material for the period ending in 1971 was that of reference 1, CPDD minutes, reports and proceedings were consulted frequently, especially after 1971.

Beginnings — The Committee on Drug Addiction

The origin of the Committee on Problems of Drug Dependence is traceable to the Bureau of Social Hygiene established in New York City in 1913 by John D. Rockefeller, Jr., to promote research in the general field of social hygiene with especial emphasis on criminology. However, because of the increasing problem of abuse of drugs*, particularly narcotics, and

*A special committee of investigation in 1919 arrived at a figure of 100 000 addicts (including cocaine abusers) in the United States.

0376-8716/89/$03.50
Printed and Published in Ireland

pressure from the public and the medical profession, the Bureau was urged to get involved in the area of drug abuse. Consequently, the Bureau of Social Hygiene established a 'Committee on Drug Addiction', whose notable accomplishments have been previously set forth in a scholarly treatise, 'The National Research Council Involvement in the Opiate Problem', authored by Nathan B. Eddy and published by the National Academy of Sciences [1].

In 1928, the newly appointed Director of the Bureau of Social Hygiene, Lawrence B. Dunham, reassessed the Bureau's involvement in the drug-addiction problem and proposed to the National Research Council, National Academy of Sciences (NRC, NAS) that this body accept funds from the Bureau for the support of a scientific investigation of narcotic drugs to be carried out under the auspices of the Division of Medical Sciences (DMS).

Accordingly, Dr. Charles White, then Chairman of DMS, with the aid and advice of four eminent members of the NRC, Drs. Claude Hudson and F.B. Laforge (chemistry) and Drs. Reid Hunt and Carl Voegtlin (pharmacology) laid the groundwork for the formation of a new 'Committee on Drug Addiction' which first met on January 12, 1929 as a 'Temporary Advisory Committee on Drug Addiction'. Dr. White was Chairman ex officio. The discussions of this group centered on elaboration of a program which would include: (1) the analysis of the chemical and biological literature of the addiction alkaloids; (2) the formulation of rules and regulations for the legitimate use of alkaloids having addiction properties and the education of physicians and the public on the knowledge of these rules by means of medical schools, scientific societies and drug-manufacturing firms and (3) the replacement of all present use of addicting alkaloids by substitutes having no addiction properties. The discussions brought forth two subjects for research: (1) the relationship between morphine and codeine (including possible dissociation of adverse and beneficial effects) and (2) the cocaine addiction problem. Little, if anything, was done at that time to address the latter problem, perhaps because the abuse of cocaine had waned considerably following the introduction of the (synthetic) substitute, procaine.

The DMS under the Chairmanship of Dr. Ludwig Hektoen (pathologist), who succeeded Dr. White as chairman of DMS on June 30, 1929, expanded the membership of the 'Temporary Advisory Committee on Drug Addiction', to include the following: Chairman, William Charles White, Consultant Pathologist, National Institute of Health and Chairman, Committee on Medical Research, National Tuberculosis Association; Charles W. Edwards, Professor of Materia Medica and Therapeutics, Chairman, Department of Pharmacology, the University of Michigan; Ludwig Hektoen, Pathologist, Director, John McCormick Institute of Infectious Diseases; Claude S. Hudson, Chief, Division of Chemistry, National Institute of Health; Reid Hunt, Professor of Pharmacology, Harvard Medical School; Frederick B. LaForge, Senior Chemist, Bureau of Entomology and Plant Quarantine, U.S. Department of Agriculture; Torald Sollman, Dean, School of Medicine and Professor of Pharmacology, Western Reserve University; Walter L. Treadway, Assistant Surgeon General, Division of Mental Hygiene, U.S. Public Health Service; Carl Voegtlin, Pharmacologist, Director, National Cancer Institute, National Institute of Health; Harry J. Anslinger, Commissioner, Bureau of Narcotics, U.S. Treasury Department and Lawrence Kolb, Assistant Surgeon General, Division of Mental Hygiene, U.S. Public Health Service.

This committee served without change until 1939. Its first meeting was held on November 3, 1929 with secretarial assistance from Mrs. Dorothy Nicolson and Mrs. Mary Goodwyn, daughters of Chairman White.

Early Scientific Program (1929—1939)

Ultimately, the Committee decided upon a research plan that involved three components — chemical, pharmacological, and clinical. The chemical effort, under the direction of Dr. Lyn-

don Small, a young, talented, Harvard-trained alkaloid chemist (who had also studied in Germany for 2 years) was begun at the University of Virginia in the autumn of 1929. Small, with his modest staff of pre- and post-doctoral students, was concerned principally with chemical modifications of the phenanthrene-type alkaloids (morphine, codeine, thebaine and neopine) occurring in opium. A complementary program on total synthesis of structures vaguely resembling morphine and congeners was directed by Erich Mosettig, Ph.D., a young organic chemist 'drafted' by Small from Professor Ernst Spaeth's laboratory, University of Vienna, Austria. Mosettig also had a small group of pre- and post-doctoral students, of which one of the authors (E.L.M.) was privileged to be a small part from 1935–1939.

Nearly a year later (June, 1930), when the need for pharmacological examination became pressing, Nathan B. Eddy, M.D., Cornell University, who had practiced medicine briefly but who, at the time, was teaching physiology and pharmacology at the University of Alberta, Edmonton, Canada was appointed to direct the pharmacology program at the University of Michigan in the laboratory of Dr. Charles Edmunds (previously mentioned Committee member).

Eddy, who had spent the 2 previous years working in the laboratory of Dr. Robert Gesell at the University of Michigan, was made Associate Research Professor of Pharmacology. He began 'baseline' animal studies of morphine and codeine covering acute toxicity and effects on pain, circulation, respiration, the G.I. tract and the CNS as reflected in overall behavior (excitement, sedation, convulsant action). Dr. Eddy's staff at Michigan in 1932 included Drs. H.M. Kruger, Charles I. Wright and R.H.K. Foster, the first in physiology at Michigan and the other two from the Universities of Rochester and Chicago, respectively. During his tenure at Michigan, Dr. Eddy also began one of his major roles in the Committee, that of liaison, with visits to the University of Virginia and other centers of activity.

Dr. Margaret Sumwalt of the Department of Pharmacology, Womens Medical College of Philadelphia, joined the staff later while Drs. Erwin E. Nelson and Ralph Smith of Dr. Edmund's departmental staff complemented the efforts of Eddy's group. Assistance was also provided by several pre-doctoral and medical students.

The clinical arm of The Committee's program began to develop about 1934 under the direction of Clifton K. Himmelsbach, M.D., a young commissioned officer of the Public Health Service from The University of Virginia Medical School. Himmelsbach, who was recruited by the aforementioned Dr. Treadway, had received research training on tolerance and physical dependence to morphine in rats at Western Reserve University under Dr. Tarold Sollmann and later, at Michigan, with Eddy. Dr. Himmelsbach began his studies with prisoner addicts at the Penitentiary Annex of the Fort Leavenworth, Kansas, Prison. This unit was shortly thereafter transferred to Lexington, Kentucky. Members of the Himmelsbach research team included Drs. Edwin G. Williams, Howard L. Andrews (later to spend many productive years at NIH), Fred W. Oberst and Ralph R. Brown. Among the substances tested by Himmelsbach (1934–1935) were codeine, isocodeine, pseudocodeine, dihydrodesoxymorphine-D (desomorphine, a new substance from Small's laboratory) and dihydromorphine, all previously studied in animals by Eddy and his colleagues.

The achievements of the first decade of Committee sponsorship can be summarized as follows. Nearly 500 compounds (the majority of them new) were supplied by Small, Mosettig and their colleagues for evaluation in animals. Three of the most promising ones, a totally synthetic compound, a tetrahydroisoquinolinophenanthrene, desomorphine and 5-methyldihydromorphinone (metopon) were studied in humans not only for dependence liability but also for pain relief. Metopon was judged to be more potent (especially orally) than morphine with less physical and psychological dependence liability but manufacturing problems precluded its distribution for general clinical

usage. Nevertheless, important structure-activity relationships evolved and Himmelsbach's basic studies for assessing tolerance and physical-dependence liability remain as a model of excellence. In addition to the studies in humans conducted at Fort Leavenworth and Lexington, clinical-efficacy trials were carried out at University Hospital, the University of Michigan by Drs. Boys, Logie and Becker (in 1938) under the supervision of Dr. Eddy, at The Pondville Cancer Hospital in Massachusetts, The Massachusetts General Hospital, at Walter Reed Army Hospital (Washington, D.C.) and at The Marine Hospital in Baltimore. In addition to Himmelsbach, a key individual in the efficacy trials was Dr. Lyndon Lee, educated at the University of Virginia and Duke University. Lee, after training with Himmelsbach, was recruited principally to test metopon. While at Pondville he conducted definitive clinical studies on morphine and desomorphine. He remained active in the analgesics area for some 40 years and maintained a liaison role with CPDD from the vantage point of Veterans Administration (VA) hospitals.

From 1929–1932, funds for Committee operations ($50 000/year) were supplied by the Bureau of Social Hygiene. For the remaining 7 years, a direct Rockefeller Foundation grant (again $50 000/year) supported the work of the Committee.

World War II hiatus

Although successes with metopon, which had definite advantages over morphine [1] and the totally synthetic isoquinolinophenanthrene, codeine-like in analgesic potency and essentially free of abuse liability (which however elicited unexpected human toxicity) [1] gave cause for optimism, it was obvious that the goals set forth by the Committee in 1929 had not been attained by 1939. Thus, plans for continuation of the scientific program were made as soon as it became apparent that Rockefeller funding would not be continued beyond 1939.

Through the influence of several people, particularly Dr. Charles White and PHS Surgeon General Thomas Parran, Small's group and Eddy joined forces at the National Institute of Health (NIH) to resume their attempts to develop safe morphine and codeine substitutes in close association with the PHS Hospital in Lexington. In the meantime, the Committee on Drug Addiction held its last meeting on January 29, 1939 and recommended to DMS that it continue a Committee on Drug Addiction in an advisory capacity (to PHS).

Ultimately (early in 1940), an advisory committee was appointed. It consisted of three members of the 1929–1939 committee: Charles White, Chairman, Harry J. Anslinger and Lawrence Kolb. Dr. Small succeeded Dr. Kolb in 1945 and Dr. Eddy was added as secretary in 1946.

Due to World War II, however, the efforts of Eddy, Small and Mosettig were diverted to the search for new antimalarials soon after the combined move to NIH. Nevertheless, partly by dint of encouragement from Dr. Eddy and the Advisory Committee, partly due to the emergence of totally synthetic analgesics (e.g., pethidine, methadone and the morphinans) from Germany and Switzerland and partly because of sustained interest in metopon, clinical studies were continued at Lexington under the direction of Himmelsbach. Dr. Himmelsbach transferred to NIH in 1944 and was succeeded as director of the Lexington facility by Dr. Harris Isbell who had served as an intern at the Lexington Hospital (1934–1935) and was a staff member at NIH until 1944. In addition, Dr. Abraham Wikler from the Staten Island Marine Hospital joined the Lexington group as a neurologist in 1940. Without a doubt, their fundamental finding that the synthetic analgesics (pethidine, methadone et al.) had dependence potential comparable to morphine was a prime factor in the strict control of these early synthetics. These synthetics had, at first, been publicized as having minimal abuse liability as morphine-like narcotics [2].

Other notable contributions of the Advisory Committee and the chemical-pharmacological research group during the war years were: (1)

introduction of metopon, particularly for oral use in chronic pain. Financial support (a metopon fund) was provided by grants from the American Cancer Society ($5000), Parke-Davis and Company and Sharpe and Dohme ($2500 each) to aid in the production and distribution of metopon; (2) preparation of a final report (by Dr. White) of the Committee's activities. This report consisted of a very large number of reprints and publications from the several participating chemical, pharmacological and clinical laboratories and was published by the NRC [3] and (3) the publication of three detailed monographs, 'The Chemistry of the Opium Alkaloids' [4], 'Studies on Drug Addiction' [5] and 'The Pharmacology of the Opium Alkaloids' [6]. It should be recorded here, too, that in June, 1939, Small and Eddy were jointly the recipients of the *first* Scientific Award of the American Pharmaceutical Manufacturers Association.

A fresh start — The Committee on Drug Addiction and Narcotics (1947—1965)

With the rapid influx of totally synthetic agents from Europe after the war and in consideration of ever-present problems of drug addiction in general, Dr. Lewis H. Weed, the Chairman of DMS, deemed it essential to form a new committee on drug abuse issues. His actions were based on requests from Surgeons General of the Army and Navy, inquiries from commercial firms and increasing emphasis on the work of the United Nations germane to public health. A further stimulus was a report brought back from Germany by a governmental committee headed by E.C. Kleiderer on research done there from 1935—1944 toward the production of totally synthetic analgesics [7]. One of the most interesting compounds described in the report was methadone (then called amidone), which, its structural dissimilarities notwithstanding, mimicked morphine in almost every aspect of its pharmacological profile.

The new committee was named the Committee on Drug Addiction and Narcotics (CDAN). Drs. Isaac Starr, Professor of Therapeutic Research, University of Pennsylvania, School of Medicine and Nathan B. Eddy, Principal Pharmacologist and Medical Officer, NIH, were appointed Chairman and Secretary, respectively. Other members of this new committee were as follows: Honorable Harry J. Anslinger, Commissioner of Narcotics, U.S. Treasury Department; Drs. Raymond N. Bieter, Professor and Head, Department of Pharmacology, University of Minnesota Medical School; Dale C. Cameron, Senior Surgeon and Assistant Chief, Division of Mental Hygiene, U.S. Public Health Service; Walter Palmer, Director, The Public Health Research Institute, City of New York; Maurice H. Seevers, Professor and Head of the Department of Pharmacology, The University of Michigan Medical School and Lyndon F. Small, Chief, Laboratory of Chemistry, National Institutes of Health. Drs. Starr and Eddy continued in their respective roles until June 30, 1960. Administrative details were handled by members of the professional staff of NRC.

The first meeting of the newly appointed committee was on October 2, 1947 at NAS, Washington, D.C. Present at this meeting were liaison representatives from the Army, Navy, FDA and the American Medical and Drug Manufacturers Association. Also attending were Drs. Weed, S.D. Aberle, D.C. Leary, Hayden C. Nicholson and Mr. John J. Lentz, Jr., representing the NRC. It was the intent of the CDAN to maintain association with these and other organizations with mutual concerns. Later, liaison was established with the World Health Organization (WHO) and the Addiction Research Foundation of Toronto.

At this time the supervised distribution of metopon was under way and would continue for 1 year. Attention was also given to developing a protocol for the international control of synthetic narcotic drugs not covered by conventions then in force. The principles of the protocol were comparable to those of the Harrison Act (also known as the Opiates Act). The Committee endorsed these principles and the protocol (later known as the Paris Protocol

of 1948) was ratified by the U.S. It provided for the same control of synthetic substances as for those of natural origin by the Geneva Convention of 1931.

From 1948–1955, a total of 15 business-scientific meetings of the CDAN were convened. After 1955 (with the exception of 1960 when the Committee met in January and April), scientific meetings were held annually, a practice which has continued to the present. The NAS-NRC published the proceedings of these meetings as 'minutes' through 1968, as 'reports' through 1974 and finally as 'proceedings' in 1975 and 1976, when NRC relinquished sponsorship. The 1977 and 1978 proceedings were published by the Committee on Problems of Drug Dependence, Inc. Starting in 1979, the proceedings have been published as part of the Research Monograph Series of the National Institute on Drug Abuse (NIDA) and are *archival.* Before 1979 they were labeled *non-archival.*

The second and third meetings of the Committee on Drug Addiction and Narcotics were, like the first, convened at NAS, Washington D.C., January 14, 1948 and May 17, 1948. At the second meeting, such items as (1) efficacy and control of methadone isomers; (2) the study of papaverine, a naturally occurring constituent of the opium plant; (3) evidence and time required to establish sufficient addiction liability to initiate narcotics control; (4) testing of K-4710 (ketobemidone, a new Demerol analog) at the Addiction Research Center (ARC); (5) clinical testing of methadone and its antipodes (at the Massachusetts General Hospital) and (6) testing of peyote at ARC and mescaline in monkeys at the University of Michigan, were discussed. One scientific paper was also presented — 'The Addiction Liability of Some Drugs of the Methadone Series and of 6-Methyldihydromorphine' by H. Isbell and Anna J. Eisenman. The major issue at the third meeting was a discussion of three research proposals seeking support from CDAN. Because of interest in supporting such types of proposals, efforts were made to establish a 'research fund' by contacting 100 members of the American Drug Manufacturers Association and 74 members of the American Pharmaceutical Manufacturers Association. Based on the replies invitations were sent to 29 drug-manufacturing firms to a meeting with the chairman and secretary of CDAN and Dr. Small. Seventeen accepted and sent representatives to Washington, D.C., on July 1, 1949. At this meeting, it was decided to invite representatives of interested firms to meet with CDAN whenever research reports were to be presented and to request the Executive Committee of NRC to authorize CDAN to solicit, accept and administer funds for research on analgesia and addiction. Authorization for a sum of $50 000 was given by NRC July 26, 1949 and, in September, Dr. Detlev Bronk, Chairman of NRC wrote to 26 drug firms inviting their support. There were 14 prompt replies. By the end of 1949, eight firms had contributed $18 500. Industrial support increased gradually until 1970 when 51 firms (eight of them foreign) donated $198 225 for the year. Also discussed at the third meeting was the possibility of clinical trials of analgesics in VA hospitals. These clinical studies were initiated some 15 years later and became an important part of the activities of the CPDD. In addition a report on K-4710 (ketobemidone, '10720') from the ARC was presented and recorded in the minutes.

The PHS hospital at Lexington, Kentucky was chosen as the site for the fourth meeting of CDAN, on October 15 and 16, 1948 to show the Committee the facilities of the hospital and measures employed for evaluating physical dependence. Dr. Henry Beecher (Massachusetts General Hospital) was invited to attend this meeting to describe his studies of analgesia and sleep in post-operative patients which was supported by a U.S. Army contract.

In line with the advisory functions of the Committee, medical research programs of the Army and VA were examined and recommendations made. The Committee also authorized a letter to the producer of ketobemidone, Winthrop Stearns, Inc., that stated that this drug, based on the results of studies conducted at Lexington, 'has addiction potentialities which are highly dangerous' and 'that clinical

application is not advisable at this time.' The Commissioner of Narcotics and the FDA were apprised of this recommendation which was accepted by the producer.

In November, 1949, March, 1950, January, 1951, June, 1951 and January, 1952, the fifth to ninth meetings of CDAN were held at NAS, Washington, D.C. Dr. Erwin E. Nelson who had attended the first two meetings as an FDA liaison representative was appointed to the Committee in the fiscal year 1948—1949 and Dr. Joseph N. Hayman, Jr., Dean of Tufts Medical College replaced Dr. Palmer in 1949.

The Committee was called upon frequently for evaluation and recommendations concerning the efficacy and dependence-producing properties of such drugs as ketobemidone, dihydrocodeinone (hydrocodone, Dicodid, Hycodan), dihydrohydroxycodeinone (oxycodone, Eucodal, Nucodan, Percodan), (±)-3-hydroxy-*N*-methylmorphinan (Dromoran) and alphaprodine (Nisentil, NU-1196), a potent Demerol (pethidine) analog. Based on results from studies conducted at Lexington, all of these drugs were judged similar to morphine regarding dependence-producing properties.

The possibility of establishing a monkey colony to perform preliminary studies on potential dependence-producing drugs at the University of Michigan was first suggested by Dr. Seevers at the fourth meeting of the Committee, October, 1948. However, his formal proposal was not considered until 1950 at the sixth meeting. The overall plan was to conduct studies in rhesus monkeys using procedures similar to those employed at Lexington for the study of 'addiction liability' in humans. The first formal reports from Dr. Seever's project (partially supported by the research fund) appeared in the minutes of the ninth and tenth meetings, both of which were held in 1952.

By 1950, there were sufficient funds from the pharmaceutical industry to partially support studies by Dr. Henry K. Beecher (Massachusetts General Hospital) whose objectives were (1) to determine the potency of analgesic agents against post-operative pain by a double-blind technique, comparing the effects of these agents with those of a placebo and the standard drug, morphine and (2) to evaluate the side effects in normal subjects of placebo, morphine and the experimental agent, randomly administered at weekly intervals.

During this period the Committee was asked to review and make recommendations on such matters as: (1) Armed Forces Medical Supply List; (2) the replaceability of opiates by available synthetic analgesics; (3) the work of WHO and its role in international control; (4) the differences among isomers in the acetylmethadol and morphinan series; (5) the development of antagonistic capabilities of nalorphine [8], the first strong, specific opioid antagonist developed (at Merck and Company in the early 1940s); (6) the demonstration of the development of tolerance and physical dependence to barbiturates; (7) the mortality of opium addicts in Taiwan; (8) the status of national and international control of narcotics; (9) criteria for clinical trial and (10) the physician's handling and care of the drug addict. Opinions and recommendations were rendered on all of these issues.

Meanwhile, chemical research by the Small-Mosettig group at NIH was redirected toward development of improved substitutes for morphine and codeine and efforts to make the U.S. independent of products from opium. All four of the above-mentioned acetylmethadol optical isomers, along with the corresponding racemates, were prepared and evaluated at NIH [9], Michigan and, in some instances at Lexington. Beginning about 1948, Eddy improved and refined the Wolff-MacDonald, hot-plate method of testing for antinociception [10] and began coordinating the NAS-sponsored, drug-testing program. The coordination of the drug testing program of the CPDD has persisted to the present at NIH.

In addition to compounds submitted by the Small-Mosettig group, the pharmaceutical industry and later, universities and other research institutions contributed compounds for preliminary testing by the hot-plate procedure for antinociception. When warranted, further testing at Michigan in monkeys was

recommended. More promising compounds could then be considered for study in humans at Lexington and/or clinical trial for analgesic efficacy.

The tenth meeting of CDAN was held at the University of Michigan, Department of Pharmacology, June, 1952 in order to observe the addiction studies in monkeys. The effects of morphine, ketobemidone, Dromoran [(±)-3-hydroxy-*N*-methylmorphinan], methadone, isomethadone, 6-methyldihydromorphine and nalorphine were shown (in morphine-dependent monkeys) 'live' and on film.

At this meeting, the Committee discussed the action of dextromethorphan (the O-methyl derivative of the analgesically inert *dextro*-isomer corresponding to Dromoran) and its potential as an antitussive agent (possible codeine substitute for cough). Also, an opinion rendered earlier by the Committee that all needs for morphine and related opiates for symptomatic pain relief could be met by then-available synthetics, was reiterated in response to a request from the Munitions Board in reference to the stockpiling of opium.

The ARC, Lexington, Kentucky was again the site for CDAN's eleventh meeting in January, 1953. Drs. Isbell, H.F. Fraser (who had been transferred to ARC from NIH in 1949) and Wikler demonstrated: (1) the abstinence syndrome after prolonged administration of morphine and attempts to relieve symptoms with synthetics; (2) the effects of prolonged administration of a new synthetic thiambutene (IC-50), distantly isosteric with methadone; (3) induction of abstinence with eserine (physostigmine) in morphine-dependent, spinal dogs; (4) abrupt and nalorphine-induced withdrawal; (5) effects of drugs and cycles of addiction and withdrawal on the electroencephalogram; (6) effect of morphine and of barbiturates on anticipatory anxiety associated with pain and (7) abstinence syndromes after withdrawal of barbiturates or alcohol.

Committee meetings that included presentation of research reports and participation of invited representatives from the pharmaceutical industry had occurred over the previous 3 years (1951–1953). It was time, it seemed, to decide whether this type of program was worthwhile and what changes, if any, should be made in the Committee's activities. Overall, it was decided that its program was sound but that rather than becoming a 'screening' facility, the Committee's efforts should be oriented toward research studies designed to contribute basic knowledge especially for the pharmaceutical industry.

Concretely, it was suggested by Dr. Isbell that Dr. Beecher's clinical trials include nalorphine-morphine combinations and nalorphine alone as a control. This suggestion to use nalorphine, the only clinically useful narcotic antagonist known at the time, was based on the idea that it might counteract the side effects of morphine in humans. Dr. Isbell's suggestion was, perhaps, promulgated by a discussion of Dr. Eddy with the group at ARC in the late 1940s about nalorphine. Dr. Eddy noted during that discussion 'that if the antagonism were really specific, the result of the administration of nalorphine to a person in whom dependence of the morphine type had been established, should be the same as for abrupt withdrawal of morphine and an abstinence syndrome should emerge'. Nalorphine was not, prior to this time, known to have analgesic action. The research (carried out by Drs. L. Lasagna and Beecher) resulted in the important finding that nalorphine itself was an effective analgesic for humans with post-operative pain. Nalorphine, then, became the first known narcotic agonist-antagonist. It was not, however, clinically useful for analgesia due to its side effects. The eventual utility of the original idea of Drs. Eddy and Isbell to test a mixture of an analgesic and an antagonist is discussed later, in the 'Animal testing' section.

The theme of the twelfth meeting, held in Boston in November, 1953 at the Massachusetts General Hospital in the historic 'Ether Dome' (where anesthesia was first demonstrated publicly), was analgesic testing in animals and humans. Attendance (76) was the largest yet and all attendees were entertained at dinner by two pharmaceutical firms. This

sponsorship gave rise to a discussion concerning propriety. With the understanding made known to the companies that no obligation was implied, it was considered acceptable to receive such amenities.

Current methods of analgesic testing were presented at this meeting along with the testing of drug mixtures, especially those for cough. The discussion of drug mixtures which could be useful as substitutes for codeine provided the stimulus for another symposium, on antitussive action. The symposium was held during the thirteenth meeting in January, 1954. The initial half day of the thirteenth meeting was at the Merck Institute for Therapeutic Research in Rahway, New Jersey. The meeting continued in the afternoon at the Hoffman-La Roche Research Laboratories, Nutley, New Jersey and concluded the following day at the New York Academy of Sciences.

In addition to the description of methods for producing cough in animals developed at Merck and Roche, reports were presented by Drs. Beecher and H.A. Bickerman, Columbia University, New York on their attempts to produce and measure cough in human volunteers. Also presented were reports by Dr. Seevers (monkey studies with coded compounds) and Dr. Isbell on research at ARC. At this meeting there was a discussion of research that the Committee might support if more funds became available. The studies mentioned were: (1) barbiturate addiction studies; (2) patient response (analgesic, subjective) to placebos; (3) difficulty of antitussive studies using volunteers and (4) the psychological aspects of the use of analgesics.

The fourteenth meeting of the Committee was another occasion for on-the-spot observation. This meeting was held on October 1 and 2, 1954 at the Sterling-Winthrop Research Institute, Rensselaer, New York, where factory production of Demerol was shown. Addiction to meperidine (Demerol), as revealed by admissions to the hospital at Lexington, was reported and the film, 'The Slave,' was presented. It was noted that medical and paramedical personnel were most susceptible to addiction to meperidine, possibly because of its availability to them.

Three new compounds were considered at the fourteenth meeting. One was the strong analgesic, 14-hydroxydihydromorphinone (Oxymorphone, Numorphan). The other two were synthetics, propoxyphene and heptazone – the latter closely, the former distantly related structurally to methadone.

At this meeting in 1954, the Committee also adopted a resolution which, in effect, expressed disapproval of a proposal by the New York Medical Society to establish clinics to dispense narcotics to addicts (with precautions), which would be in reality a quasi-legalization of their distribution. This was an unequivocal rejection of maintenance therapy, an attitude that was to change some 15 years later, as is well known.

For its fifteenth meeting, CDAN met again in Lexington, Kentucky, at the PHS Hospital in January, 1955. Various aspects of treatment of addicts were discussed. Continued support of Seevers and Beecher was approved, as was a new grant for analgesic studies at Sloan-Kettering Memorial Institute, New York by Dr. Raymond Houde. Also, an application from Dr. Lyndon Lee at Wayne County Hospital, Detroit for clinical studies of analgesics was approved in principle. These applications followed an announcement in *Science* (November, 1954) that CDAN might have available limited resources for support of research on analgesia and addiction. Included in this announcement was a request for information on basic research being carried out in these areas, so that the Committee might serve as a center for exchange of information on current investigations in analgesia and addiction. Incidentally, this was the only meeting from 1930–1971 not attended (due to illness) by Dr. Eddy.

From September, 1955 to February, 1965 meetings 16–27 (two in 1960) of CDAN were held (for dates and sites, see Appendix 3, Table 2 of Ref. 1). Changes in membership during this period were as follows: Dr. Marshall Gates, Chairman of The Department of Chemistry, University of Rochester succeeded Dr. Small who died in 1957. Added to the Committee the

same year was Dr. Jonathan Cole, formerly a member of the NRC professional staff and Chief of the Psychopharmacology Center of The National Institute of Mental Health. Drs. Cameron and Nelson resigned in 1958 and were replaced by Drs. Ralph Smith (FDA), mentioned previously and Henry Brill of the New York State Department of Mental Health and Director of The Pilgrim Psychiatric Hospital on Long Island. Mr. Anslinger resigned from the Committee in 1959 and, although close liaison with The Bureau of Narcotics was maintained, he was not replaced by anyone from the Bureau. Dr. Starr, whose tenure as Chairman was the longest (13 years) ever, stepped down (but remained a Committee member until 1969). He was replaced as Chairman by Dr. Eddy for 1 year only (1961), because he (Dr. Eddy) was made a professional associate of NRC and (officially) designated Executive Secretary of CDAN, duties which he had been performing for several years. Dr. Cameron who served on the Committee from 1947–1958 and again in 1961, became Chairman in 1962, a position he held until 1967 when he resigned to assume the office of Chief, Drug Dependence, WHO, Geneva, Switzerland. In this position he maintained close ties with the Committee until his retirement from WHO (1975). Other new members of the Committee in the next 3 years were: Everette L. May, Ph.D., Chemist, Chief, Section on Medicinal Chemistry, NIH; Isidor Chein, Ph.D., Psychologist, New York University Graduate School of Arts and Sciences; Francis N. Waldrop, Ph.D., Behavioral Scientist, St. Elizabeth's Hospital, Washington, D.C.; Harris Isbell, M.D., Clinical Pharmacologist, Department of Medicine, University of Kentucky Medical Center, who had retired from PHS in 1963; and Robert Strauss, Ph.D., Behavioral Scientist, University of Kentucky. Dr. Chein retired in 1964 after serving for 2 years.

The decade from 1955 to 1965 was probably among the most eventful in the Committee's history. Growing awareness of and interest in, the scientific sessions were reflected by an increasing attendance and diversity of reports presented especially from 1961–1965. A subscription dinner became an established custom along with an after-dinner speaker presenting a lecture of general interest to the attendants.

The research fund grew steadily from an annual contribution of $39 000 in 1955 (one foreign, 26 domestic firms contributing) to $85 349 (four foreign, 33 domestic) in 1965. This was supplemented by annual contributions from the VA ($5000–$7500) and WHO ($2000) beginning in 1961. Consequently, grant applications and funding increased. These are all described in detail on pp. 74–79 of Ref. 1. Most of the projects were funded for 1–5 years, but support of Drs. Seevers and Houde continued throughout the 10-year period and for many years beyond.

New, noteworthy drugs evaluated by CDAN during this period were propoxyphene (a distant relative of methadone); the hexamethyleneimines (e.g., ethoheptazine); the benzimidazoles (e.g., etonitazene); the 6,7-benzomorphans [11] (which spawned, among others, phenazocine, SKF 10047 and cyclazocine); fentanyl, and the antidiarrheal compound, diphenoxylate. Also, dihydrocodeine, marketed in Europe for many years as an antitussive agent, was tested clinically for analgesic efficacy by Beecher and was found to be effective with minimal side effects. Several of these drugs are in medical use today and are controlled as narcotics partly as a result of the findings and recommendations of CDAN. Two drugs which were not controlled at that time, dextropropoxyphene (Darvon), the (+)-isomer of propoxyphene and pentazocine (Talwin), the latter, the first agonist-antagonist to be used clinically, were controlled later. In fact it was during this decade that the basic laboratory research of Archer, Harris et al. [12] and the clinical studies of Beecher, Keats, Lasagna et al. [13] paved the way for the heightened interest in and the rapid development of the agonist-antagonist type analgesics.

Specific opioid antagonists developed by the pharmaceutical industry and tested thoroughly by CDAN from 1957–1965 were levallorphan, a nalorphine-like morphinan derivative; a 'pure' antagonist, naloxone (*N*-allylnoroxymorphone)

and its orally effective, longer-acting, cyclopropylmethyl analog, naltrexone. These three compounds along with nalorphine have been of inestimable value in the dependence studies at Michigan and Lexington. They have also been important drugs in clinical practice and have stimulated a great deal of basic research in the receptor area. Naltrexone was finally approved for clinical use by the FDA in 1984.

It was during this period, too, that seminal analgesic-efficacy studies by Houde, Wallenstein, Rogers et al. [14] became models of excellence and that clinical trials by the VA under the direction of Dr. Lyndon Lee on potentially useful analgesics were begun. This period (1955—1965) was also characterized by acknowledgement of the importance of the monkey colony at Michigan not only as a first-class 'screening' facility but which was also rapidly developing into a laboratory of excellence in many aspects of basic research on analgesics, their antagonists and the agonist-antagonists. Assisting Dr. Seevers in this effort were graduate students, Samuel Irwin and Gerald Deneau, who received their doctoral degrees in the Department of Pharmacology, University of Michigan.

The Bureau of Narcotics and the FDA were increasingly seeking the advice and recommendations of CDAN on efficacy and abuse liability of potentially marketable drugs. From time to time resolutions and statements were issued by the Committee regarding narcotics control, treatment of addiction and replaceability of codeine and other opiates by synthetics. The abuse of psychotropic substances such as the amphetamines, tranquilizers, etc. was discussed from time to time but no research was sponsored by the Committee in this regard. In 1963 the Committee co-authored with The Council on Mental Health, American Medical Association, a paper, 'Narcotics in Medical Practice: The Use of Narcotic Drugs in Medical Practice and The Medical Management of Narcotic Addicts' [15].

Finally, some important changes in personnel at ARC should be noted. Drs. Isbell and Wikler retired in 1963 to accept positions at the University of Kentucky, while Dr. Fraser went to Eli Lilly. This would have been a crushing blow were it not for the appointment of Dr. William Martin (who had joined ARC in 1957) with M.S. and M.D. degrees from The University of Illinois, to succeed Isbell as Director and the hiring of Charles Gorodetzky (M.D., Boston University School of Medicine, Ph.D., University of Kentucky) and Donald R. Jasinski (M.D. from The University of Illinois, Chicago) in 1963 and 1965, respectively. These three maintained the splendid scientific tradition established by their predecessors.

The Committee on Problems of Drug Dependence (1965—1976)

In 1964 the WHO Expert Committee on Addiction-Producing Drugs met to discuss (among other subjects) terminology relating to drug abuse. Objections to the term 'addiction' had been expressed by Isbell (who preferred 'chronic intoxication') as early as 1956 and by Seevers (1962) who alluded particularly to the effects of amphetamines as psychotoxic. The Expert Committee ultimately recommended 'drug dependence' as a substitute for 'drug addiction' and 'drug habituation' with a modifying phrase to indicate the drug type (e.g., morphine type, cocaine type, etc.). The CDAN accepted this recommendation and officially changed its name to Committee on Problems of Drug Dependence (CPDD) on July 1, 1965, a title which more accurately reflected a broadening scope of interests.

From 1966 to 1973 contributions from the pharmaceutical industry increased from $101 850 to nearly $200 000 (51 domestic and eight foreign firms), leveled at the latter figure through 1973 and gradually declined thereafter. These funds were supplemented from 1961—1970 by contractual and grant monies from the VA, Office of Civilian Defense, FDA and WHO (whose last contribution of $2000 was in 1966). From 1971—1976, contributions also came from The Bureau of Narcotics and Dangerous Drugs (BNDD), The National Institute of Mental Health and The National Institute on Drug Abuse (NIDA).

Needless to say, the grants program flourished during the halcyon funding years of 1966 to 1973, principally in the clinical area. Investigators included, in addition to the redoubtable Ray Houde and his capable associates, Stanley Wallenstein and Ada Rogers, such outstanding researchers as Henry K. Beecher, Louis Lasagna, Arthur Keats, T.J. De Kornfeld, L.J. Cass, F.F. Snyder, T.J. Kantor and the VA study group (Lyndon Lee, Richard Paddock, J.W. Belleville, William Forrest, Colin Brown et al.) [16]. Those funded in the basic research areas included R. Aston, L.S. Harris, H.L. Grumbach, R.T. Harris and G.A. Deneau. Dr. Deneau, Senior Investigator in Dr. Seevers dependence studies in monkeys from 1954–1965, assisted by S. Weiss, established a dog colony dependent upon sodium barbital, for assessing the abuse potential of hypnotics and sedatives. Deneau set up a similar Beagle-dog colony at The Southern Research Institute in Birmingham, Alabama and reported to the Committee through 1971 [17].

Noteworthy, too, is that (1) in 1969, CPDD held its first (joint) meeting with The Committee on Alcohol and Drug Dependence, Council on Mental Health of the AMA at Palo Alto; (2) in 1970 the first interim meeting of the executive committee was convened to allow more time for discussion of special problems and (3) in 1971 CPDD met outside the United States for the first time (in Toronto, Canada at The Addiction Research Foundation).

At the first interim meeting, functions of CPDD were redefined by Dr. R. Keith Cannan, Chairman of DMS-NAS from 1953–1967 and Executive Secretary of CPDD from 1967–1970. These functions included support of the Annual Meeting and publication of its proceedings, the screening and evaluation programs and the grants program. CPDD also functioned in an advisory role to The Bureau of Narcotics.

Peak attendance (459) at the annual scientific meetings was reached in 1970 at The Hilton Hotel in Washington, D.C., February 16–18. Complete and accurate information on time, place and attendance of meetings (to 1971), on resources (to 1970) and on the grants program (to 1972) are given in Tables 2, 3 and 4, respectively, of Ref. 1.

During 1965–1976 (especially the later years) CPDD continued to advise The Bureau of Narcotics [later becoming the Bureau of Narcotics and Dangerous Drugs (BNDD), then the Drug Enforcement Administration (DEA)] and FDA on various aspects of drug dependence. It again aided The Council on Mental Health, AMA, in revising (1967, 1971) [15] the 1963 statement on 'Narcotics in Medical Practice'. Included were recommendations on the Nyswander–Dole 'Methadone Maintenance' program [18]. In collaboration with the AMA Committee on Alcoholism and Drug Dependence, it drafted a resolution on marihuana (see Ref. 1 therein, p. 116) and provided a task force which issued a report to FDA regarding the abuse potential and hazards of drug combinations (Ref. 1, p. 119). A 'Statement on Testing for Dependence Liability in Animals and Man' was prepared and made an *Addendum to the Minutes* of the 28th meeting in 1966. At the request of The United Nations Division of Narcotics, this was published in The United Nations Bulletin on Narcotics in 1969. A completely revised statement was published in 1972 [19].

In 1971 attention was again focused on replaceability of the narcotic analgesics and antitussives from natural origin. The opinion, that opium was expendable, was again expressed.

In 1967 Dr. Eddy (who had retired from but remained a consultant for NIH in 1960) resigned as Executive Secretary and was succeeded by the aforementioned Dr. Cannan. Dr. Eddy also relinquished management of the testing program to one of the authors (E.L.M.) but remained a member of CPDD until 1971 and a consultant until his death in 1973. Executive Secretary Cannan was succeeded by Mr. Duke Trexler, an employee of NAS, in 1971. Mr. Trexler, assisted by an associate executive secretary, Dr. Ralph Smith who had for many years been associated with committee activities, served until the end of NAS sponsorship in

Table I. Members of the Committee on Problems of Drug Dependence[a] and Consultants in 1972.

H. Frank Fraser, Chairman	
D.C. Trexler, Executive Secretary (NRC)	
R.G. Smith, Associate Executive Secretary (NRC)	
Henry Brill	Harris Isbell
Jonathan O. Cole	Lewis J. Sargent
Daniel X. Freedman	Cecil G. Sheps
Leo E. Hollister	Klaus R. Unna
Raymond W. Houde	E. Leong Way
Milton H. Joffe	Chris Zarafonetis
Consultants	
Nathan B. Eddy	Everette L. May
William R. Martin	Maurice H. Seevers

[a]At the time of the Annual Meeting for the denoted year.

1976. The members of the CPDD from 1972 to 1976 are listed in Tables I–V.

Regarding chairmanships, Dr. Henry Brill, a member of CPDD since 1960, became chairman in 1968, succeeded, as stated before, by Dr. Eddy for 1 year. Dr. H. Frank Fraser, well known for his distinguished career at NIH, ARC and Eli Lilly, also served for a single year, followed by Dr. Leo Hollister, a member of CPDD since 1969. An outstanding medical investigator from the VA Hospital, Palo Alto, Dr. Hollister functioned very effectively in this capacity through the difficult transition years to be addressed below.

Table II. Members of the Committee on Problems of Drug Dependence and Consultants in 1973.

Leo E. Hollister, Chairman	
D.C. Trexler, Executive Secretary	
R.G. Smith, Associate Executive Secretary (NRC)	
Jonathan O. Cole	Lee N. Robins
Daniel X. Freedman	Lewis J. Sargent
Raymond W. Houde	Cecil G. Sheps
Donald R. Jasinski	Klaus R. Unna
Milton H. Joffe	E. Leong Way
Beny J. Primm	Chris Zarafonetis
Herbert A. Raskin	
Consultants	
Henry Brill	Everette L. May
H. Frank Fraser	Maurice H. Seevers

Table III. Members of the Committee on Problems of Drug Dependence and Consultants in 1974.

Leo E. Hollister, Chairman	
D.C. Trexler, Executive Secretary (NRC)	
R.G. Smith, Associate Executive Secretary (NRC)	
Jonathan O. Cole	Beny J. Primm
Daniel X. Freedman	Lee N. Robins
Raymond W. Houde	Cecil G. Sheps
Donald R. Jasinski	E. Leong Way
Milton H. Joffe	Chris Zarafonetis
Consultants	
Henry Brill	Everette L. May
H. Frank Fraser	Maurice H. Seevers

Table IV. Members of the Committee on Problems of Drug Dependence in 1975.

Leo E. Hollister, Chairman	
D.C. Trexler, Executive Secretary (NRC)	
R.G. Smith, Associate Executive Secretary (NRC)	
Daniel X. Freedman	Jack H. Mendelson
Louis S. Harris	Beny J. Primm
Raymond W. Houde	Herbert A. Raskin
Arthur E. Jacobson	Lee N. Robins
Donald R. Jasinski	Cecil G. Sheps
Milton H. Joffe (deceased)	Travis Thompson
Everette L. May	Klaus R. Unna

Table V. Members of the Committee on Problems of Drug Dependence in 1976

Leo E. Hollister, Chairman	
D.C. Trexler, Executive Secretary (NRC)	
R.G. Smith, Associate Executive Secretary (NRC)	
Daniel X. Freedman	Beny J. Primm
Louis S. Harris	Herbert A. Raskin
Raymond W. Houde	Lee N. Robins
Arthur E. Jacobson	Cecil G. Sheps
Donald R. Jasinski	Travis Thompson
Everette L. May	Klaus R. Unna
Jack H. Mendelson	

At the University of Michigan [20], the monkey-dependence studies were in the capable charge of Dr. Julian Villarreal from 1967–1973. Dr. Villarreal a medical doctor from Mexico City, Mexico, received the Ph.D. degree from the University of Michigan (in 1969) and had assisted Dr. Deneau for a year until the latter moved to Birmingham. From 1973–1974,

Henry H. Swain, M.D. assisted him and became the principal investigator from 1974–1978, followed by James H. Woods, Ph.D., who is presently in charge of the group.

At the thirty-fourth annual meeting of CPDD held on March 22–24, 1972 at the University of Michigan, Ann Arbor, John E. Ingersoll, Director of BNDD, in his formal remarks to Committee attendants stated, that 'drastically reducing the availability of heroin is our major objective,' while generally implying that the abuse of narcotics was reaching major proportions. Further emphasizing this, he called attention to the establishment of the White House Special Action Office on Drug Abuse Prevention, headed by Dr. Jerome Jaffe (an eminent investigator in drug abuse) and to the methadone maintenance program and treatment programs that Jaffe was implementing.

Following the Michigan meeting, BNDD considered the heroin-abuse problem so serious that this body negotiated a contract with NAS-CPDD to conduct a study concerning the use of synthetic substitutes for the opiate narcotics in medicine and the possibility of banning opium production. Consultants chosen for this study were Drs. Louis Harris and Joseph Cochin, talented researchers in drug abuse and intimately associated with CPDD activities. Their survey (from December 1972 to March 1973) ultimately involved the AMA and the results were published by The Drug Abuse Council, Inc., 1828 L. Street, Washington, D.C. 20036, under the title, 'Synthetic Substitutes for Opiate Alkaloids: A Feasibility Study.' The summary statement was as follows: 'There is reason to believe that banning of opium production will not significantly affect problems of narcotic abuse even if adequate substitutes for the opium-derived drugs were available'.

There were at least two other notable events at the 1972 meeting. One was the presentation of a paper by Dr. William Martin and Virginia Sandquist of ARC, entitled 'Long-Acting Narcotic Antagonists.' They suggested that such antagonists or depot preparations of antagonists might provide blockade of the usual heroin effects and thus could be a treatment modality for heroin abuse. Their findings have been explored with enthusiasm and some clinical success. The second event of especial note at the 1972 meeting was the convening of the first satellite conference at a CPDD annual meeting. This session on drug self-administration (Chairman, Dr. James H. Woods of Dr. Seevers group) led to a CPDD-sponsored workshop held in February, 1973 on 'Standardization of Self-Administration Techniques in Animals.' The chairmen were Drs. Duncan McCarthy of The Parke-Davis Company, Ann Arbor, Michigan and Woods. The proceedings of this workshop were published in the first newsletter of The International Study Group Investigating Drugs as Reinforcers (ISGIDAR) in August, 1973. This group has continued to convene satellite meetings at each annual meeting of CPDD and undoubtedly helped pave the way for inclusion of the testing of stimulants and depressants as a part of CPDD's broadened interests and activities in 1988. Furthermore, several distinguished members of ISGIDAR (Drs. Woods, Schuster, Balster, Brady, Mello, Mendelson, Thompson, Griffiths et al.) eventually became valuable members of the CPDD.

Early in 1973, Dr. Nathan Browne Eddy who had been the kingpin, the major driving force of the Committee almost from its inception (and especially from 1947), died peacefully in his sleep after a full workday of scientific and other activities. It was fitting and timely, therefore, that at the May 21–23, 1973 annual meeting in Chapel Hill, North Carolina, Chairman Leo Hollister appointed an ad hoc committee (Seevers, Brill and Fraser) to establish a Nathan B. Eddy Memorial Award. This committee sent its recommendations to Dr. Hollister on August 10, 1973 providing for an annual award based on contributions to the drug abuse field either for 'an unusually important discovery or for total contributions over the entire career of the recipient'. The award, to be presented at the annual meeting, was to consist of a gold medal and a cash prize of $2500 plus travel expenses. Also recommended were an International Award Committee of six persons to be selected by CPDD to serve a 3-year term and a goal of

$75 000 to be obtained through solicitations from manufacturers, friends of Nathan Eddy and attendees at recent and possibly future CPDD meetings. The recommendations in essence were accepted and appropriately the first Eddy awardee was Dr. Seevers at the annual meeting of CPDD, held in Mexico City, March 14–17, 1974. The 1975 and 1976 recipients of the award were ARC–University of Kentucky stalwarts, Harris Isbell and Abraham Wikler, respectively. The subsequent awardees are listed in Table XXV.

In executive session at the 1969 meeting in Palo Alto, it was noted that reports from Michigan on monkey-dependence studies were being issued 8–12 months after receipt of compounds. This lag was due not only to an increasing rate of submission of compounds but also to the more sophisticated and exhaustive tests being made, in turn a reflection of changes in the pharmacological profile of the new drugs, particularly the agonist-antagonists.

To ensure more prompt reporting and to generally complement the Michigan program, a primate colony modeled after that at Michigan was ultimately established in 1973 at The Medical College of Virginia (MCV) of Virginia Commonwealth University under the direction of Dr. Louis S. Harris (assisted by Dr. W.L. Dewey, for many years a collaborator at Sterling-Winthrop Research Institute and The University of North Carolina) who, a year earlier had been appointed Chairman, Department of Pharmacology at MCV. Dr. Mario Aceto, who had joined the MCV staff from Winthrop, was in charge of the day-to-day testing-research operations and another MCV staff member Dr. Robert Balster, recruited from Duke University in 1973, supervised self-administration studies on drugs of special interest. Financially, the MCV program was made possible because first BNDD and then the National Institute of Mental Health assumed support of the Michigan studies. Ultimately (starting in 1978), the National Institute on Drug Abuse (NIDA) provided most of the financial support for both the Michigan and the MCV primate programs to which was later added (at MCV) rodent-infusion tests for dependence potential. The coordination of effort and agreement of results in cases of deliberate duplication have been remarkable and gratifying. In retrospect this move was timely because it coincided with the gradual slowdown and ultimate cessation (December 31, 1976) of human testing for abuse potential at ARC. It was important to have a more complete animal testing program to compensate for the lack of human data.

The last annual meeting of CPDD to be held at NAS was in May, 1975. Attendance (445) at this meeting was the second largest in the history of The Committee. In addition to the three-day scientific program, four coordinate satellite meetings were scheduled. At the executive session (May 18), a goal of $100 000 was set as *principal* for the Eddy award. At this session, also, the groundwork was laid for a conference on prediction of abuse liability of stimulant and depressant drugs. Such a conference, convened at NAS April 19–21, 1976, was sponsored by CPDD, NAS-NRC, DEA, FDA and NIDA with representatives of some thirty pharmaceutical firms in attendance. Co-chairmen of the conference were Drs. Travis Thompson and Klaus Unna of The University of Minnesota and University of Illinois, Chicago, respectively, both members of the Executive Committee of CPDD. Participants were internationally recognized investigators in drug abuse. The proceedings, titled 'Predicting Dependence Liability of Stimulant and Depressant Drugs', were published by University Park Press, Baltimore, London, Tokyo, 1976. Co-editors were Thompson and Unna. This was a valuable supplement to the previously mentioned publication (recently revised a second time) 'Testing for Dependence Liability in Animals and Man' [19].

The death knell of NAS sponsorship of CPDD was sounded at its interim meeting at the NAS building, February 26, 1976. Chairman Hollister made public the contents of a letter (dated December 9, 1975) written to him by Thomas J. Kennedy, M.D., Executive Director of The Assembly of Life Sciences, NRC-NAS. In essence the letter stated that the Executive

Committee of the Assembly of Life Sciences had voted to discontinue sponsorship of CPDD by approximately June 30, 1976. This decision was based on the recommendation of a 'Visiting Committee' appointed by NRC-NAS to review various aspects of the Academy-Committee structure.

Despite the consternation caused by this decision, the Committee began immediately to debate other possibilities for continuation of its activities, feeling unanimously that CPDD 'serves an essential purpose in the national interest and the agencies that have provided support in the past have, in informal discussion, expressed their wish to continue support'.

Of the eight possibilities considered, incorporation of CPDD as a separate entity was decided upon. Thus, it was declared that CPDD would be incorporated under the laws of the District of Columbia, by June 30, 1976 if possible. This was not achieved, whereupon NAS agreed to extend sponsorship to February, 1977. Along with incorporation would be solicitation of a consortium of 8–10 highly regarded scientific societies with interest in drug abuse; each society would name one of its members to serve on a Board of Directors.

The NAS also agreed to publish the Proceedings of the Annual Meeting to be held in Richmond, Virginia and to lend its good offices to the solicitation of funds for the fiscal year 1977. The NAS aided in every way possible the attainment of an orderly transition.

At the last NAS-sponsored annual meeting of CPDD (hosted by The Medical College of Virginia, Virginia Commonwealth University) in June, 1976, three satellite meetings were held: Conference on Naltrexone, Chairman, Dr. Julius Demetrios, Division of Research, NIDA, Rockville, Maryland; Drugs as Reinforcers, Chairman, Dr. Charles R. Schuster, The University of Chicago; Session on Drugs as Discriminative Stimuli, Chairman, Dr. John A. Rosecrans, MCV. There were over 400 in attendance at this meeting. In addition to a plenary session at which Dr. Abraham Wikler gave the Eddy-Award address, some 52 scientific papers were presented. Following a reception and banquet dinner, scholarly addresses were presented by Dr. Jerome Jaffe, then Professor of Psychiatry, College of Physicians and Surgeons, Columbia University, New York and Dr. Robert L. DuPont, Director of NIDA.

Among the last drugs to be tested at ARC in humans were meptazinol, nalbuphine, buprenorphine, butorphanol, propoxyphene napsylate, propiram fumarate and tilidine. Most of these drugs were also tested for clinical efficacy by various CPDD grantees, principally by Ray Houde's group and the VA. Most are now marketed.

Post NRC — an independent, incorporated committee (1976—1989)

The two extraordinary events which occurred late in 1976 deeply affected the future course of the CPDD. The traumatic effects of the loss of the human testing facilities at the Addiction Research Center (ARC) in Lexington, Kentucky (due to a moratorium on prisoner research declared by the Federal Bureau of Prisons) and the loss of NAS-NRC sponsorship colored the events of the following several years as well as the contemporary activities of the CPDD. These incidents heralded the beginning of a tumultuous decade in the life of the Committee.

Upon retrospective evaluation, it was realized that the impact of the CPDD on the human testing facilities at Lexington had appreciably lessened during the past several years, coincident with the ARC's status as the intramural research arm of NIDA. NIDA had been mandated to test only those compounds which were of interest to the U.S. Government (not necessarily compounds which might be marketed by the pharmaceutical industry and for which the CPDD perceived a need to determine abuse liability in human subjects with the thought that these new opioids might pose a public health problem). Furthermore, the ability of the CPDD to influence or even suggest which compounds might be evaluated at the Lexington facility had lessened considerably since Dr. Eddy's death. Thus, the CPDD, coincident with its

incorporation as a separate entity, began a search for an alternative to the Lexington facilities.

The activities of the Committee following incorporation were complex and extensive. These activities are grouped for purposes of discussion into: (1) incorporation and reorganization, (2) purposes and goals, (3) animal testing, (4) human testing, (5) relationships with U.S. Government and international organizations, (6) funds and awards and (7) conversion to a membership organization.

Incorporation and reorganization

The first meeting of the wholly independent Committee on Problems of Drug Dependence, Inc., was held at the International Inn in Washington, D.C., in February, 1977. The primary objective was to organize the CPDD, Inc., and to elect officers for the new corporation to meet the legal requirements for the Committee to act as an independent entity under a consortium of professional societies.

The initial and continuing reorganization of the CPDD will be presented in a simplified manner. It may, even so, seem complex because, since incorporation in 1977, the CPDD, Inc., had to modify its by-laws many times to enable the organizational structure to best fit its needs. The apparent complexity was confounded by two facts: (1) The retention of the word 'Committee' in its name. After incorporation, the 'Committee' became in fact a Corporation, but the old word was retained. Thus, an Executive Committee, various standing and ad hoc committees and subcommittees of the 'Committee' were eventually formed; (2) The rapid evolution of the CPDD, Inc., in its attempt to increase the depth and the breadth of its views far beyond those encompassed by the original CPDD, before incorporation. Presently, at least four new members are elected to the Board each year (as noted below, the present-day Board is the combination of an Executive Committee and a Board of Directors), and this serves to infuse new views and thoughts into its actions.

The CPDD, Inc., in 1977, divided its structure into an Executive Committee and a Board of Directors. These two groups constituted the Corporation, and the offices of President of the Corporation and Chairman of the Board were created. Although these could have been, in principle, two separate individuals, in fact the Chairman of the Board of Directors served as the President of the Corporation. New members of the Executive Committee were elected from a list of candidates selected by a subcommittee and each member of the Board of Directors was a representative of a professional society, appointed (with the concurrence of the Executive Committee) by that society. The professional organizations were called the Affiliated Societies of the CPDD, Inc.

Dr. Leo Hollister was elected Chairman of the Executive Committee and Dr. Theresa Harwood the Executive Secretary of the Corporation, at the time of incorporation. Dr. Hollister was succeeded as Chairman of the Executive Committee in July, 1977, by Dr. Daniel X. Friedman. Dr. Hollister then served (until July, 1979) as the Chairman of the Board of Directors. The members of the Committee and the initial four Affiliated Societies at the time of incorporation are noted in Table VI.

Table VI. Members of the Committee on Problems of Drug Dependence, Inc., and Affiliated Societies in 1977.

Leo E. Hollister, Chairman	
Theresa Harwood, Executive Secretary	
Daniel X. Freedman	Beny J. Primm
Louis S. Harris	Herbert A. Raskin
Raymond W. Houde	Lee N. Robins
Arthur E. Jacobson	Cecil G. Sheps
Donald R. Jasinski	Travis Thompson
Everette L. May	Klaus R. Unna
Jack H. Mendelson	

Affiliated Societies

American Psychiatric Association
American Society for Pharmacology and Experimental Therapeutics
American Society for Clinical Pharmacology and Therapeutics
American College of Neuropsychopharmacology

During the next several years, the National Medical Association, the Society for Behavioral Medicine, the American Chemical Society, the American Sociological Association, the American Medical Association and the American Psychological Association also became affiliated with the CPDD, Inc. At the present time, all of these scientific organizations except the American Sociological Association continue as sponsors of the independent Committee. Each of the affiliated societies appointed a representative to an enlarged Board of Directors.

Dr. E. Leong Way was elected as Chairman of the Board of Directors in 1978, replacing Dr. Hollister who had officially retired as a member of the CPDD, Inc. Dr. Keith F. Killam was elected as the Secretary and Treasurer of the Board. Dr. Hollister returned to the Committee as the Executive Secretary of the corporation in July, 1979, replacing Dr. Harwood. The members of the CPDD and the affiliated societies, from 1977 to the present are listed in Tables VI to XVIII. The Tables reflect the membership at the time of the Annual Meeting for the denoted year.

Table VII. Members of the Executive Committee and the Board of Directors of the CPDD, Inc., in 1978.

Daniel X. Freedman, Chairman	
Theresa Harwood, Executive Secretary	
Joseph Cochin	Jack H. Mendelson
Louis S. Harris	John O'Donnell
Arthur E. Jacobson	Beny J. Primm
Jerome H. Jaffe	Herbert A. Raskin
Donald R. Jasinski	Lee N. Robins
Arthur S. Keats	Travis Thompson
Everette L. May	

Board of Directors

Daniel X. Freedman, American Psychiatric Association
Leo E. Hollister, American Society for Clinical Pharmacology and Therapeutics
Keith F. Killam, American College of Neuropsychopharmacology
Everette L. May, American Chemical Society
Herbert A. Raskin, American Medical Association
E. Leong Way, American Society for Pharmacology and Experimental Therapeutics

Table VIII. Members of the Executive Committee and the Board of Directors of the CPDD, Inc., in 1979.

Joseph Cochin, Chairman	
Leo E. Hollister, Executive Secretary	
Joseph V. Brady	Arthur S. Keats
Troy Duster	Harold Kalant
Charles W. Gorodetzky	Everette L. May
Louis S. Harris	Jack H. Mendelson
Theresa Harwood	John O'Donnell
Arthur E. Jacobson	Charles R. Schuster
Jerome H. Jaffe	Henry H. Swain

Board of Directors

E. Leong Way, Chairman, American Society for Pharmacology and Experimental Therapeutics
Daniel X. Freedman, American Psychiatric Association
Keith F. Killam, American College of Neuropsychopharmacology
Everette L. May, American Chemical Society
Edward C. Senay, American Medical Association
Beny J. Primm, National Medical Association
James A. Woods, American Psychological Association
Raymond W. Houde, American Society for Clinical Pharmacology and Therapeutics

Table IX. Members of the Executive Committee and the Board of Directors of the CPDD, Inc., in 1980.

Joseph Cochin, Chairman	
Leo E. Hollister, Executive Secretary	
Joseph V. Brady	Arthur S. Keats
Troy Duster	Harold Kalant
Charles W. Gorodetzky	Everette L. May
Louis S. Harris	Jack H. Mendelson
Theresa Harwood	Charles R. Schuster
Arthur E. Jacobson	Henry H. Swain
Jerome H. Jaffe	

Board of Directors

E. Leong Way, Chairman, American Society for Pharmacology and Experimental Therapeutics
Daniel X. Freedman, American Psychiatric Association
Keith F. Killam, American College of Neuropsychopharmacology
Everette L. May, American Chemical Society
Edward C. Senay, American Medical Association
Beny J. Primm, National Medical Association
James A. Woods, American Psychological Association
Raymond W. Houde, American Society for Clinical Pharmacology and Therapeutics

Table X. Members of the Executive Committee and the Board of Directors and Permanent Liasion of the CPDD, Inc., in 1981.

Joseph Cochin, Chairman
Leo E. Hollister, Executive Secretary

Joseph V. Brady	Arthur S. Keats
Troy Duster	Harold Kalant
Charles W. Gorodetzky	Everette L. May
Louis S. Harris	Jack H. Mendelson
Theresa Harwood	Charles R. Schuster
Arthur E. Jacobson	Henry H. Swain
Jerome H. Jaffe	

Board of Directors

E. Leong Way, Chairman, American Society for Pharmacology and Experimental Therapeutics
Raymond W. Houde, American Society for Clinical Pharmacology and Therapeutics
Daniel X. Freedman, American Psychiatric Association
Keith F. Killam, American College of Neuropsychopharmacology
Everette L. May, American Chemical Society
Edward C. Senay, American Medical Association
Beny J. Primm, National Medical Association
James A. Woods, American Psychological Association

Permanent Liaison

Louis S. Harris
Arthur E. Jacobson

Table XI. Members of the Executive Committee and the Board of Directors and Permanent Liaison of the CPDD, Inc., in 1982.

Joseph V. Brady, Chairman
Joseph Cochin, Executive Secretary

Martin W. Adler	Theresa Harwood
Sidney Archer	Leo E. Hollister
William T. Beaver	Jerome H. Jaffe
Richard J. Bonnie	Harold Kalant
Theodore J. Cicero	Charles P. O'Brien
Troy Duster	Charles R. Schuster
Charles W. Gorodetzky	Henry H. Swain

Board of Directors

E. Leong Way, Chairman, American Society for Pharmacology and Experimental Therapeutics
Raymond W. Houde, American Society for Clinical Pharmacology and Therapeutics
Keith F. Killam, American College of Neuropsychopharmacology
Everette L. May, American Chemical Society
Jack H. Mendelson, American Psychiatric Association
Beny J. Primm, National Medical Association
Lee N. Robins, American Sociological Association
Edward C. Senay, American Medical Association
James A. Woods, American Psychological Association

Permanent Liaison

Louis S. Harris
Arthur E. Jacobson

In order to gather scientists representing the diverse scientific disciplines encompassed by the CPDD's continued emphasis on 'physical dependence potential and abuse liability', and its attempt to realize its goals and purposes, the Executive Committee continued to expand its membership, reaching a plateau of 18 voting members by 1987. Although scientists elected to the Executive Committee had been limited to a 3-year term under the auspices of the NAS, the Incorporated Committee, in principle, increased the term to four years and consecutive election to a second term was barred.

At its inception in 1977, the members of the Board of Directors were limited to a 5-year term of office. The ability of the sponsoring organization to reappoint its representative to consecutive terms was, initially, unlimited. Acceptance of the representative suggested by the affiliated society to the Board of Directors of the CPDD was, however, the prerogative of the Executive Committee.

In the beginning, the Board of Directors and the Executive Committee of CPDD, Inc., were assigned different roles. The Board of Directors had the responsibility of guiding the Executive Committee and suggesting new endeavors, while the Executive Committee was the implementing arm of the organization. This separation in roles essentially disappeared over the following decade as will be described below and the by-laws of the CPDD were modified in 1987 to reflect the fact that, whether appointed or elected, individuals were functionally equivalent in their work on the Committee.

The Incorporated Committee continued the policy of holding two meetings a year, an interim meeting in December and a second meeting in conjunction with the Annual Scien-

Table XII. Members of the Executive Committee and the Board of Directors of the CPDD, Inc., in 1983.

Leo E. Hollister, Chairman
Joseph Cochin, Executive Secretary

Martin W. Adler	Lloyd D. Johnston
Sidney Archer	Mary Jeanne Kreek
William T. Beaver	William R. Martin
Richard J. Bonnie	Roger E. Meyer
Theodore J. Cicero	Charles P. O'Brien
Marian W. Fischman	Akira E. Takemori
Roland R. Griffiths	Julian E. Villarreal
Donald R. Jasinski	

Board of Directors

Beny J. Primm, Chairman, National Medical Association
Joseph V. Brady, Society of Behavioral Medicine
Raymond W. Houde, American Society for Clinical Pharmacology and Therapeutics
Keith F. Killam, American College of Neuropsychopharmacology
Everette L. May, American Chemical Society
Jack H. Mendelson, American Psychiatric Association
Lee N. Robins, American Sociological Association
Edward C. Senay, American Medical Association
E. Leong Way, American Society for Pharmacology and Experimental Therapeutics
James A. Woods, American Psychological Association

Table XIII. Members of the Executive Committee and the Board of Directors of the CPDD, Inc., in 1984.

Leo E. Hollister, Chairman
Joseph Cochin, Executive Secretary

Martin W. Adler	Donald R. Jasinski
Sidney Archer	Lloyd D. Johnston
William T. Beaver	Mary Jeanne Kreek
Richard J. Bonnie	William R. Martin
Theodore J. Cicero	Roger E. Meyer
William L. Dewey	Charles P. O'Brien
Marian W. Fischman	Akira E. Takemori
Roland R. Griffiths	

Board of Directors

Beny J. Primm, Chairman, National Medical Association
Joseph V. Brady, Society of Behavioral Medicine
Raymond W. Houde, American Society for Clinical Pharmacology and Therapeutics
Keith F. Killam, American College of Neuropsychopharmacology
Everette L. May, American Chemical Society
Jack H. Mendelson, American Psychiatric Association
Lee N. Robins, American Sociological Association
Edward C. Senay, American Medical Association
E. Leong Way, American Society for Pharmacology and Experimental Therapeutics
James A. Woods, American Psychological Association

Table XIV. Members of the Executive Committee and the Board of Directors of the CPDD, Inc., in 1985.

Theodore J. Cicero, Chairman
Joseph Cochin, Executive Secretary

Martin W. Adler	Lloyd D. Johnston
Thomas F. Burks	John Kaplan
William L. Dewey	Conan Kornetsky
Loretta P. Finnegan	Mary Jeanne Kreek
Marian W. Fischman	William R. Martin
Roland R. Griffiths	Roger E. Meyer
Leo E. Hollister	Akira E. Takemori
Donald R. Jasinski	

Board of Directors

Beny J. Primm, Chairman, National Medical Association
Joseph V. Brady, Society of Behavioral Medicine
Raymond W. Houde, American Society for Clinical Pharmacology and Therapeutics
Keith F. Killam, American College of Neuropsychopharmacology
Everette L. May, American Chemical Society
Jack H. Mendelson, American Psychiatric Association
Lee N. Robins, American Sociological Association
Edward C. Senay, American Medical Association
E. Leong Way, American Society for Pharmacology and Experimental Therapeutics
James A. Woods, American Psychological Association

Table XV. Members of the Executive Committee and the Board of Directors of the CPDD, Inc., in 1986.

Mary Jeanne Kreek, Chairman
Theodore J. Cicero, Past Chairman
William L. Dewey, Chairman-Elect
Joseph Cochin (deceased), Executive Secretary

Martin W. Adler	Donald R. Jasinski
Thomas F. Burks	Lloyd D. Johnston
Richard A. Deitrich	John Kaplan
Loretta P. Finnegan	Conan Kornetsky
Marian W. Fischman	Horace H. Loh
Roland R. Griffiths	Akira E. Takemori
Leo E. Hollister	

Board of Directors

Beny J. Primm, Chairman, National Medical Association
Joseph V. Brady, Society of Behavioral Medicine
Raymond W. Houde, American Society for Clinical Pharmacology and Therapeutics
Keith F. Killam, American College of Neuropsychopharmacology
Everette L. May, American Chemical Society
Jack H. Mendelson, American Psychiatric Association
E. Leong Way, American Society for Pharmacology and Experimental Therapeutics
James A. Woods, American Psychological Association

Table XVI. Members of the Executive Committee and the Board of Directors of the CPDD, Inc., in 1987.

Mary Jeanne Kreek, Chairman
Theodore J. Cicero, Past Chairman
William L. Dewey, Chairman-Elect
Martin W. Adler, Executive Secretary

Mitchell B. Balter	John Kaplan
William T. Beaver	Sheppard G. Kellam
Thomas F. Burks	Herbert D. Kleber
Richard A. Deitrich	Conan Kornetsky
Loretta P. Finnegan	Horace H. Loh
Marian W. Fischman	Edward C. Senay
Roland R. Griffiths	Akira E. Takemori
Donald R. Jasinski	

Board of Directors

Keith F. Killam, Chairman, American Society for Pharmacology and Experimental Therapeutics
James A. Woods, Secretary-Treasurer, American Psychological Association
Joseph V. Brady, Society of Behavioral Medicine
Kathleen M. Foley, American Society for Clinical Pharmacology and Therapeutics
Everette L. May, American Chemical Society
Jack H. Mendelson, American Psychiatric Association
Beny J. Primm, National Medical Association
E. Leong Way, American College of Neuropsychopharmacology

Table XVII. Members of the Board of the CPDD, Inc., and affiliated societies in 1988.

William L. Dewey, Chairman
Thomas F. Burks, Chairman-Elect
Mary Jeanne Kreek, Past Chairman
Joseph V. Brady, Secretary/Treasurer
Keith F. Killam, Chairman, Advisory Council
Martin W. Adler, Executive Secretary

Robert L. Balster	Herbert D. Kleber
Mitchell B. Balter	Conan Kornetsky
William T. Beaver	Horace H. Loh
Richard A. Deitrich	Everette L. May
Loretta P. Finnegan	Donald E. McMillan
Kathleen M. Foley[a]	Nancy K. Mello
Louis S. Harris	Jack H. Mendelson
Reese T. Jones	Beny J. Primm
John Kaplan	Edward C. Senay
Sheppard G. Kellam	E. Leong Way

Affiliated Societies

American Chemical Society
American College of Neuropsychopharmacology
American Psychiatric Association
American Psychological Association
American Society for Clinical Pharmacology and Therapeutics
American Society for Pharmacology and Experimental Therapeutics
National Medical Association
Society of Behavioral Medicine

[a]Retired from Board in April, 1988. Replaced by Donald R. Jasinski.

tific Meeting in the Spring or early Summer. In order to facilitate the decision-making process of the Committee on a daily basis, an executive working group, or Action Committee, was formally constituted at an interim meeting in 1979. The President and the Executive Secretary of the Corporation, and the Chairman of the Executive Committee, became the members of the Action Committee at that time. With the revision of the by-laws in 1985 (under the guidance of a very active Rules Committee, with Dr. Charles Gorodetzky as Chairman of that standing subcommittee) the Chairman, Chairman-elect and Past-chairman of the Executive Committee, the Secretary/Treasurer and the Chairman of the Board of Directors (later, the Advisory Council) and the Executive Secretary of the Corporation became the constituents of the Action Committee. In 1985, the membership of the Corporation was restated as being only those individuals who were members of the then Board of Directors (who were, now, to be appointed to a 4-year term by the affiliated societies with the concurrence of the membership of the Corporation), and the members of the Executive Committee, who continued to be elected to a 4-year term. This definition clarified the positions of subcommittee chairmen, some of whom were not members of either the Executive Committee or the Board of Directors, and the status of the Executive Secretary of the Corporation which, in 1986, became a salaried position. These subcommittee chairmen and the Executive Secretary of the Corporation were not, then, voting members of the Corporation. The offices formerly titled Chairman of the Board of Directors and President of the Corporation were combined, and the positions of Chairman of the

Table XVIII. Members of the Board of the CPDD, Inc., and affiliated societies in 1989.

William L. Dewey, Chairman
Thomas F. Burks, Chairman-Elect
Mary Jeanne Kreek, Past Chairman
Joseph V. Brady, Secretary/Treasurer
Keith F. Killam, Chairman, Advisory Council
Martin W. Adler, Executive Secretary

Robert L. Balster	James M. Kulikowski
Mitchell B. Balter	Horace H. Loh
William T. Beaver	Donald E. McMillan
Thomas J. Crowley	Nancy K. Mello
Richard A. Deitrich	Jack H. Mendelson
Loretta P. Finnegan	Beny J. Primm
Louis S. Harris	Kenner C. Rice
Donald R. Jasinski	Edward C. Senay
Reese T. Jones	Eric J. Simon
Sheppard G. Kellam	E. Leong Way
Herbert D. Kleber	

Affiliated Societies

American Chemical Society
American College of Neuropsychopharmacology
American Psychiatric Association
American Psychological Association
American Society for Clinical Pharmacology and Therapeutics
American Society for Pharmacology and Experimental Therapeutics
National Medical Association
Society of Behavioral Medicine

Table XIX. Standing Committees and Liaison members of the Committee on Problems of Drug Dependence, Inc., in 1983.

Committee Chairmen
Charles W. Gorodetzky, Rules
Louis S. Harris, Scientific Meetings
Arthur E. Jacobson, Drug Testing Program

Permanent Liaison
Jerome H. Jaffe, Veterans Administration
Howard McClain, Drug Enforcement Administration
Heinz Sorer, National Institute on Drug Abuse
Edward C. Tocus, Food and Drug Administration

Table XX. Standing Committees and Liaison members of the Committee on Problems of Drug Dependence, Inc., in 1984 and 1985.

Committee Chairmen
Charles W. Gorodetzky, Rules
Louis S. Harris, Scientific Meetings
Arthur E. Jacobson, Drug Testing Program

Permanent Liaison
Harold Kalant, Addiction Research Foundation (Toronto)
Howard McClain, Drug Enforcement Administration
Heinz Sorer, National Institute on Drug Abuse
Edward C. Tocus, Food and Drug Administration

Table XXI. Standing Committees and Liaison members of the Committee on Problems of Drug Dependence, Inc., in 1986.

Committee Chairmen
Charles W. Gorodetzky, Rules
Louis S. Harris, Scientific Meetings
Arthur E. Jacobson, Drug Testing Program

Permanent Liaison
Jerome H. Jaffe, National Institute on Drug Abuse
Harold Kalant, Addiction Research Foundation (Toronto)
Howard McClain, Drug Enforcement Administration
Charles P. O'Brien, Veterans Administration
Boris Tabakoff, National Institute on Alcohol Abuse and Alcoholism
Edward C. Tocus, Food and Drug Administration

Table XXII. Standing Committees and Liaison members of the Committee on Problems of Drug Dependence, Inc., in 1987.

Committee Chairmen
Theodore J. Cicero, Animal Testing Committee
Marian W. Fischman, Human Testing
Charles W. Gorodetzky, Rules
Louis S. Harris, Scientific Meetings
Arthur E. Jacobson, Drug Testing Program

Permanent Liaison
Harold Kalant, Addiction Research Foundation (Toronto)
Howard McClain, Drug Enforcement Administration
Charles R. Schuster, National Institute on Drug Abuse
Boris Tabakoff, National Institute on Alcohol Abuse and Alcoholism
Edward C. Tocus, Food and Drug Administration

Table XXIII. Standing Committees and Liaison members of the Committee on Problems of Drug Dependence, Inc., in 1988 and 1989.

Committee Chairmen
Theodore J. Cicero, Animal Testing Committee
Marian W. Fischman, Human Testing
Charles W. Gorodetzky, Rules
Louis S. Harris, Scientific Meetings
Arthur E. Jacobson, Drug Testing Program

Permanent Liaison
Harold Kalant, Addiction Research Foundation (Toronto)
Howard McClain, Drug Enforcement Administration
Charles R. Schuster, National Institute on Drug Abuse
Boris Tabakoff, National Institute on Alcohol Abuse and Alcoholism
Francis J. Vocci, Food and Drug Administration

Executive Committee, Past-chairman, and Chairman-elect were clarified with this revision of the by-laws. As a result of these modifications, in 1985 a 16-member Executive Committee was defined, with the Past-chairman as a 17th member. Two appointed members of the Board of Directors served as voting members of the Executive Committee in the Corporation, to legitimize the corporate structure of the organization according to the laws of the District of Columbia, where the CPDD incorporated. During that meeting in 1985, it was decided to limit the term of all subcommittees to 1 year. A further change in the structure of the Committee was initiated during the 1985 Interim Meeting when Dr. Kreek appointed Dr. Burks as chairman of a subcommittee to examine the functions of the separate Board of Directors of CPDD in relation to the functions of the Executive Committee and the overall operations of the corporate organization of CPDD. Members of the Corporation were polled for opinions in January, 1986, and the responses were summarized at a meeting in San Francisco on May 17, 1986, of Drs. Burks, Kreek, Killam and Gorodetzky. On this basis, specific recommendations for changes in the CPDD, Inc., by-laws were made that would join the Board of Directors and the Executive Committee into a combined Board of the CPDD, Inc., all of whom would be voting members of the Corporation. The Chairman of the former

Table XXIV. Site of the Annual Meeting of the Committee on Problems of Drug Dependence.

Year	Date	Place	Annual Scientific Meeting No.
1972	May 22–24	Univ. of Michigan, Ann Arbor, MI	34
1973	May 21–23	Univ. of North Carolina, Chapel Hill, NC	35
1974	March 10–14	El Camino Real Hotel, Mexico City, Mexico	36
1975	May 19–21	National Academy of Sciences, Wash., DC	37
1976	June 7–9	Richmond Hyatt House, Richmond, VA	38
1977	July 6–9	Hyatt Regency Hotel, Cambridge, MA	39
1978	June 3–6	Lord Baltimore Hotel, Baltimore, MD	40
1979	June 4–6	Holiday Inn, Center City, Philadelphia, PA	41
1980	June 16–19	Dunfey Hyannis Hotel, Hyannis, MA	42
1981	July 12–15	San Franciscan Hotel, San Francisco, CA	43
1982	June 27–30	Sheraton Centre Hotel, Toronto, Canada	44
1983	June 12–15	Hyatt Regency Hotel, Lexington, KY	45
1984	June 4–6	Chase Park Plaza Hotel, St. Louis, MO	46
1985	June 10–12	Hyatt Regency Hotel, Baltimore, MD	47
1986	June 16–18	Granlibakken Resort, Tahoe City, CA	48
1987	June 15–19	Adam's Mark Hotel, Philadelphia, PA	49
1988	June 29–July 1	Seacrest Resort, North Falmouth, MA	50
1989	June 19–22	Keystone Resort, Keystone, CO	51[a]

[a]Sixtieth anniversary of the CPDD (1929–1989).

Table XXV. Committee on Problems of Drug Dependence award winners.

	Nathan B. Eddy Memorial Award
1974	Maurice H. Seevers
1975	Harris Isbell
1976	Abraham Wikler
1977	William R. Martin
1978	Hans W. Kosterlitz
1979	Eddie L. Way
1980	Avram Goldstein
1981	Everette L. May
1982	Vincent P. Dole and Marie Nyswander
1983	Eric J. Simon
1984	Raymond W. Houde
1985	Louis S. Harris
1986	Harold Kalant
1987	Clifton K. Himmelsbach
1988	Albert Herz
1989	Leo E. Hollister
	J. Michael Morrison, Jr., Award
1982	Robert Petersen
1984	Kay Croker
1986	Edward Tocus
1988	Marvin Snyder
	Joseph Cochin Young Investigator Award
1987	Michael Bozarth
1988	Frank Porreca
1989	Errol B. DeSouza

Board of Directors would become the Chairman of the Advisory Council (Dr. Killam). This Advisory Council was to be made up of the former members of the Board of Directors, those members appointed as representatives of the Affiliated Societies. The report of the subcommittee was presented for discussion at the June, 1986, Annual Meeting in Tahoe City by Dr. Gorodetzky. In June, 1987, at the Annual Meeting, the Executive Committee accepted the revision to the by-laws. At that point there could be a maximum of 25 voting members of the combined Board, including the Chairman (Dr. Kreek), chairman-elect (Dr. Dewey), Past-chairman (Dr. Cicero), Secretary/Treasurer (Dr. Woods), and the aforementioned Chairman of the Advisory Council. There were, also, three standing subcommittees with chairs that reported to the Board (Dr. Gorodetzky, Rules, Dr. Harris, Scientific Meetings, and Dr. Jacobson, Drug Testing Program) and five liaison members. A complete list of the standing subcommittees and the liaison members is given in Tables XIX to XXIII. As noted previously, in July, 1986, the office of Executive Secretary became a paid position, and Dr. Martin W. Adler was elected to that position.

In 1987, two additional standing subcommittees were created, the Animal Testing Committee (Dr. Cicero, Chairman) and the Human Testing Committee (Dr. Fischman, Chairman). Thus, the changes in the makeup of the CPDD which were initially slow have come much more rapidly, a hectic pace compared with the early years of the CPDD, to the point where consideration of the conversion of the CPDD to a membership organization, an idea first introduced by Dr. Adler during the Annual Meeting in 1984, and reformulated in ensuing years, became an almost acceptable idea. At the 1988 Annual Meeting (see Table XXIV for sites of annual meetings from 1972 – 1989), the Board overwhelmingly voted against the motion that the CPDD should not change and that it should remain as a non-membership organization, but the possible reformation of the CPDD as a membership organization was left for further consideration and discussion at future meetings. In anticipation of the goal of expanded membership, an alumni association composed of the former members of the CPDD was established as an affinity group at the Interim Meeting in 1986, and Dr. Hollister was chosen as the first President of that group.

Contributions to the Incorporated Committee from pharmaceutical companies, to enable the CPDD to meet its purposes and goals slowly diminished after the extraordinary year of 1973. In 1977, 26 industrial groups contributed $144 900 but by 1985, the figure had declined to $80 000. Contributions from industrial groups have recently increased with the institution of a new CPDD stimulant/depressant animal test program. However, since 1978, NIDA has absorbed much of the considerable cost of both the animal testing activities for the opioid programs at the University of Michigan and the Medical College of

Virginia, and the Johns Hopkins University work on stimulants and depressants. NIH has absorbed the major costs of the work at NIH, NIDDK (National Institute of Diabetes and Digestive and Kidney Diseases), for the coordination of the opioid program. Grants from the CPDD to the groups at UM, MCV, and NIDDK have helped to supplement the U.S. Government funding and, presently, the CPDD provides all of the funds to run the Committee's program on the determination of the physical dependence potential and abuse liability of stimulants and depressants at three universities (The University of Chicago, the Medical College of Virginia, and the University of Michigan). The development of the stimulant/depressant program will be discussed more fully in the section on 'Animal testing'.

Purposes and goals of the incorporated committee

It is perhaps surprising that the overall goals and purposes of the CPDD have endured since the inception of the organization in 1929, although the emphasis on certain facets of the work of the Committee has changed, and a few modifications of the original purposes have been made. These purposes have expanded over the decades to meet current concerns of drug abuse.

The goals of the newly reorganized Committee were noted at the November 9, 1978 meeting to be: (a) to conduct an annual scientific meeting; (b) to facilitate the screening of new psychoactive agents that might be abused; (c) to facilitate communication between the animal testing facilities at Richmond and Ann Arbor and (d) to try to obtain means for testing dependence liability in humans.

The Goals and Guidelines subcommittee, a committee which was initially formed to formulate the Goals of the CPDD, Inc., for the 1978 meeting, was reconstituted at times during the ensuing 7 years to restudy the purposes of the CPDD, Inc. Thus, three goals of the Incorporated Committee were articulated during the December, 1985, Interim Meeting (Dr. Mary Jeanne Kreek, Chairman). The goals were: (1) to nurture, promote and carry out abuse liability research and testing, both at the preclinical and clinical levels, (2) to sponsor an annual scientific meeting in fields related to drug abuse and chemical dependency and (3) to serve as advisor to both the public and private sectors, nationally and internationally (to our government, the World Health Organization, industry and academia). It has been noted that the annual scientific meeting has become one of the few forums where scientists from diverse disciplines can discuss problems of drug abuse and drug dependence at a rigorous academic and scientific level. It is evident that a marked change in the annual scientific meeting began about 1987 as evidence by the increased number of symposia and the dramatically increased breadth of coverage. The duration of the meeting has also increased, from an initial length of two and a half days to an anticipated four days in 1989.

Relationships with governmental organizations

Although governmental representatives had been guests at CPDD meetings since its inception, formal liaison membership in the CPDD with governmental organizations was established in 1979 with Edward Tocus, Heinz Sorer and Howard McClain as the appointed representatives of the FDA, NIDA and the DEA, respectively. More recently, these agencies were joined by the NIAAA and the Addiction Research Foundation in Toronto. Recent efforts, initiated in 1981 and discussed at the 1982 Annual Meeting in Toronto by Dr. Inayat Khan (presently Chief, Psychotropic and Narcotic Drugs, Division of Drug Management and Policies, WHO) and fairly continuously thereafter, to enable the incorporated Committee to become a Collaborative Center with the World Health Organization, have neared fruition.

The efforts of the CPDD to serve as advisor to the public sector both nationally and internationally have not lessened since it became independent, but with the institutionalization of advisory committees to the various govern-

ment agencies concerned with drugs of abuse, the efforts have been modified. Examples of the contemporary CPDD approach to the advisement of agencies are manifold. In 1984 the CPDD published, in a NIDA research monograph, an updated document, 'Testing Drugs for Physical Dependence Potential and Abuse Liability' [21] a revision of Ref. 19. The document was noted by Dr. Tocus to be valuable for the FDA as a model and guide for gathering data. Two years later, during the 1986 Interim Meeting, Dr. Tocus mentioned that the CPDD guidelines for testing presented in that document were used when guidelines were requested of the FDA by industrial groups.

In addition, a number of meetings have been held under CPDD auspices to discuss issues of interest to government groups. A special FDA/NIDA/CPDD/pharmaceutical company meeting was organized by Drs. Jaffe, Gorodetzky, Mendelson and Hollister. This symposium entitled 'Prediction of Human Abuse Potential of Drugs' was held in Washington, D.C., April 9, 1978. In 1979, CPDD supplied a liaison (Dr. Senay) to the subcommittee of the FDA Drug Abuse Advisory Council to discuss the clinical testing of neuropeptides and homologs, including opioid peptides. At the 1982 Annual Meeting a committee was appointed to report to NIDA on the domestic need for thebaine and the justification of increased production of hydromorphone (co-chaired by Drs. Archer and Cochin). In response to proposed congressional legislation concerning the use of animals in research, in 1982 at the Interim Meeting in San Juan, the CPDD formed an Animal Legislation subcommittee with Dr. Killam as Chairman, for support of a commission to study the use of animals in research, emphasizing the continued usefulness and necessity of these animals for this research. Several CPDD position papers have been written and a great deal of discussion has occurred at various CPDD meetings since that time concerning groups which oppose the use of animals for research.

In 1983, Dr. Pollin, then Director of NIDA, enunciated his desire to work closely with CPDD and to use its advice and assistance. During that meeting the Committee noted that the data obtained by the assessment of physical dependence potential and abuse liability in animals by the Drug Testing Program of the CPDD could be considered as a facet of prevention research, and these data could be used by the FDA and the DEA to control the marketing of new products on a national basis thereby preventing the inadvertent introduction of substances adversely affecting public health. For example, methylenedioxymethamphetamine (MDMA), an illicit stimulant, was being used for patients by some psychiatrists and apparently was being abused by a number of individuals. There was concern that the side effects of MDMA were more devastating than usually noted with amphetamine-like substances. Thus MDMA was examined by the CPDD's drug testing groups [22] at the request of NIDA. The results of the testing of this controlled-substance analog clearly indicated that this drug had significant abuse potential. These data led to the emergency placement of MDMA under Schedule I of the Controlled Substances Act by FDA.

During the post-NRC period, much greater emphasis has been given to drugs other than opioids. Cocaine abuse has, once again, become a difficult problem and a concern for government organizations involved in drug abuse prevention in the 1980s. New drugs, such as phencyclidine (PCP), are illicitly introduced to the public and abused from time to time, but the older drugs, the opioids and various of the stimulants and depressants, reach peaks of popularity followed by periods of decline in their usage. This ongoing historical cycle has been found, thus far, to be difficult to prevent. Research into the causes of the abuse, the nature and effect of these drugs in humans, and the prevention of their introduction to the public, continue to be among the main reasons for the continuance of the existence of the CPDD as an organization and its continuous cooperation with government organizations concerned with drug abuse. There has, of late, been discussion in Congress on the legalization of certain of these drugs of abuse as one method of

dealing with their illicit supply. At the 1988 Annual Meeting in Cape Cod, the members of the Committee noted their disagreement with the idea of legalization of opioids, cocaine and certain other abused substances, and suggested that this be conveyed to Mr. Charles Rangell, Chairman of the House Select Committee on Narcotics, and to his Chief of Staff, Mr. Jurith, by Dr. Dewey. The CPDD's stand on this issue was summarized by Mr. Kaplan at that 1988 meeting. He noted that although legalization would be likely to cut the rate of crimes caused by these substances, public health problems would increase.

The increased prevalence of licit and illicit use of stimulants and depressants by the public during this period induced the CPDD to initiate its new testing program on determination of the dependence potential and abuse liability of these classes of compounds. This program is discussed more fully below, but the considerable concern of the CPDD with these classes of abused substances should be noted in regard to CPDD initiatives and relationships with government organizations. Thus, during the Interim Meeting in 1986, in Washington, D.C., a consensus meeting (with ASPET) was planned on cocaine research. The document ('Scientific Perspectives on Cocaine Abuse') relating to this meeting was produced for presentation to ADAMHA (Alcohol, Drug Abuse and Mental Health Administration) and its components, including NIDA, and was published [23].

As a further example of the cooperation of the CPDD with government organizations during the post-NRC period, the Drug Testing Committee of the CPDD has tested a number of fentanyl derivatives [24–35] which were synthesized under contract by NIDA at the request of the DEA, or obtained directly from the DEA. Some of these fentanyl derivatives were found to be among the most potent opioids ever tested and to have dependence potential of the morphine type. Even the most potent of them, fortunately, could be antagonized by a conventional dose of naloxone. Lately, a fentanyl analogue, carfentanil, introduced by a company for animal use, was examined by the drug-testing groups of the CPDD at the behest of NIDA and the FDA and was found to be 25 000 times as potent as morphine as an antinociceptive in rodents [33]. It also, like the other potent fentanyl analogues, could be antagonized by naloxone. The CPDD noted during its discussion of this drug that the introduction of carfentanil as a Schedule II drug could constitute a danger to the public health by diversion of the licit supply; however, it was further noted, diversion from licit suppliers is much less of a threat to the public than synthesis of this extremely potent drug by illicit manufacturers.

The post-NRC period has also been one which has seen a great deal of interaction between the CPDD and the WHO. The CPDD has sent a representative to many of the Expert Committee on Drug Dependence and Program Planning Working Group (PPWG) meetings held during this time in Geneva, at the behest of Dr. Khan, of the WHO. Dr. L. Harris was the CPDD representative to the International Conference on Drug Abuse and Illicit Trafficking which was held in Vienna in June, 1987. This has allowed CPDD input into important policy and decision-making activities of the WHO with respect to international control of drug abuse, prevention, identification and prediction of drug-abuse liability, and in the control of existing clinical, drug-abuse related problems. Further, cooperation with the WHO has been manifested by the CPDD's testing of many of the stimulants and depressants which were being considered for scheduling by WHO. The scientific data obtained from the drug-testing groups of the CPDD has been noted by Dr. Khan to be of great value to the WHO for their scheduling responsibilities under the Psychotropic Convention since few, if any, other groups are able to provide such scientific data to them within a reasonable time.

Although the WHO has not been able to provide consistent funding for this testing, in 1979 a $12 000 grant from the United Nations Fund for Drug Abuse Control was given to the CPDD through WHO to test khat (*Catha edulis*,

Forsk.), a plant which was known to contain various bioactive components such as cathine ((+)-norpseudoephedrine), cathinone (α-aminopropiophenone) and other, more complex, alkaloids. It was noted in the *Bulletin on Narcotics* [36] that questions related to *Catha edulis* were first raised at the international level in 1935 at the League of Nations. The effect caused by chewing the leaves and stem tips of the khat plant, a plant with mild stimulant and euphoric properties, had become a concern for various African and Mid-Eastern countries (e.g., Kenya, the Yemen Arab Republic) and for the WHO, who feared that its use would spread to other continents. The CPDD provided funding, obtained from the WHO grant for these tests, to Dr. Knoll in Hungary, to the Medical College of Virginia and to The University of Chicago, and to Dr. Yanagita in Japan and Dr. Halbach, formerly of WHO. Work on the isolation and characterization of the bioactive alkaloids was undertaken at NIH by Dr. Henry M. Fales (Chief, Laboratory of Chemistry, NHLBI), an expert in mass spectrometry, and by Drs. May and Jacobson at NIDDK (then NIAMDD). Dr. K. Szendrei, a Hungarian chemist (presently on the staff of the United Nations Division of Narcotic Drugs, Vienna), who was at that time attached to the UN staff in Geneva, brought the khat plant to Dr. May's laboratory at NIH for the purpose of this investigation and was instrumental in the characterization of several bioactive constituents of the plant.

In response to the request of the WHO for information about agonist-antagonists to be discussed at the PPWG in Geneva, the CPDD sponsored the Innisbrook Symposium on Narcotic Antagonist Analgesics which was held in Tarpon Springs, Florida, in February, 1983, with Dr. Harris as Chairman. A CPDD position paper was prepared for the WHO. Papers on the subjects encompassed by the Symposium were published in *Drug and Alcohol Dependence* [37] in 1985 as an up-to-date review of the field, edited by Drs. Schuster and Harris.

A symposium to discuss the scientific evidence on the abuse liability of 28 stimulants and hallucinogens [38] under consideration by the WHO for international control was organized as an adjunct to the Annual Scientific Meeting of the CPDD in June, 1984, in St. Louis. As noted by Drs. James H. Woods and Charles R. Schuster in their foreword [39] to the published symposium in *Drug and Alcohol Dependence* [40], the CPDD 'thought it would be helpful to all parties concerned, WHO, the United Nations Commission on Narcotic Drugs, pharmaceutical companies, and the academic community to have an open forum for discussion of the complex issues that go into decision-making on the international control of dependence-producing substances. To the extent that pertinent information is made more open to the scrutiny of all, decisions to control substances with abuse liability may be more informed.'

During the Third World Conference on Clinical Pharmacology and Therapeutics in Sweden in 1986, the CPDD collaborated with Dr. Khan and the WHO in the organization of a symposium entitled 'Drug Dependence: Benefit-Risk Ratio Assessment of Agonist-Antagonist Analgesics'. Several members of the CPDD or their close associates (Drs. Harris, Woods, and Lasagna) spoke at this symposium, and the papers which were presented were published [41] in *Drug and Alcohol Dependence*, edited by Drs. T. Yanagita and C. Johanson.

Animal testing

It is interesting to remember that from its initiation the pharmacological testing facilities under the auspices of the Committee have not only served as a 'screening' facility, but have had a distinct research orientation. This concept and implementation of a screening facility biased towards research led, for example, to the testing of combinations of opioids and their antagonists. Drs. Beecher and Houde initiated the testing, for pain-relief efficacy, of various ratios of mixtures of morphine and nalorphine in the early 1950s. Dr. Harris Isbell studied the effects of these mixtures on non-tolerant former morphine addicts at the Addiction Research Center in Lexington, Kentucky [42]. Various ratios of morphine and SKF 10 047 were tested at the University of Michigan in

1962 [43]. Although the results from the work were not immediately applied, it should be noted that there is now at least one such combination which has recently been introduced and successfully marketed. Pentazocine (Talwin) had been found to be abused by a segment of the addict population in some geographic areas from about 1977 to the early 1980s, especially in combination with an antihistamine, tripelennamine. To eliminate the intravenous abuse of pentazocine, Sterling-Winthrop reformulated it with naloxone, a narcotic antagonist. This was reported to the CPDD by Drs. George Goldstein and Frank Rosenberg at the Interim Meeting in December 1982. At the Annual Meeting in 1984, Dr. Glenda Treadway noted that a special symposium would be presented during that meeting sponsored by Winthrop-Breon, a subsidiary of Sterling Drugs, called 'Talwin NX One Year Later' with several members of the CPDD making presentations (Drs. Jasinski, Harris, and Senay). It was noted at that meeting that the parenteral abuse of pentazocine had diminished appreciably since the introduction of Talwin NX.

The idea of combining a narcotic antagonist with an agonist, which resulted in the successful combination of pentazocine and naloxone in Talwin NX, might be attributed to the extensive early work of researchers who tested mixtures of agonists and antagonists in animals and humans in testing facilities run under the auspices of the CPDD. That work illustrates the type of accomplishment which resulted from the CPDD's 'screening' of analgesics in a research-oriented mode, and epitomizes the far-reaching consequences of such research. The ostensibly simple screening/research effort of the testing groups associated with the CPDD has continued since that time, resulting in a number of valuable contributions to the field by these groups. Their work continues to be published annually in the Proceedings of the Annual Scientific Meeting of the CPDD.

Opioid testing program

The original purposes of the program have not been modified since its inception by Dr. Eddy, although the beneficiaries of the program, the nature and number of tests which are carried out, and the groups which have run the testing procedures under the auspices of the CPDD have changed considerably over the decades. This program has served, and continues to serve, to alert individuals and government organizations to the possibility of public health problems and issues arising from the marketing, licit or illicit, of new compounds which affect the various opioid-receptor systems. The individual laboratories in the consortium that examine compounds under the auspices of the Committee are noted below.

Constituency of the opioid testing program

The Drug Testing Program on opioid-like compounds serves three distinct audiences:

(1) University researchers who seek to determine whether, and how well, their new compounds interact with an opioid receptor. These in vitro data, and data obtained from rodent antinociceptive and narcotic antagonist assays, are utilized for qualitative or quantitative structure-activity relationship studies. Occasionally, when a sufficient amount of sample is received, data from single-dose suppression and precipitated-withdrawal assays are obtained for this constituency.

(2) Pharmaceutical firms that wish to determine the physical dependence potential and abuse liability of their compounds as part of their preclinical work with compounds which have the ability to interact with opioid receptors. The FDA has, on occasion, requested such data from industrial firms prior to marketing in order to prevent public health problems and to facilitate scheduling.

(3) Government organizations, such as the DEA and the WHO, who desire sufficient in vivo data for scheduling purposes, nationally or internationally.

Procedures used in the opioid testing program

Compounds have been, and continue to be, tested in a 'blind' fashion. Only the Chairman of the Drug Testing Program (Dr. A. E. Jacobson, NIDDK, NIH), who assigns an NIH coded num-

ber to the compound, is aware of the name and structure of the tested compound before the data gathered under CPDD auspices are released for publication. At the Annual Meeting in July, 1977, the incorporated Committee decided to place a three-year time limit on the confidentiality of the data obtained under CPDD auspices. Within the next few years a further decision was made requiring the submission of spectroscopic and analytical information with each compound, to enable the Chairman of the Drug Testing Program to verify that the compound appeared to have the assigned structure and was sufficiently pure for testing. The purity of submitted samples is evaluated, before and after testing them, through thin-layer chromatography by Dr. Everette L. May (at MCV).

All but one of the rodent studies are carried out at the Medical College of Virginia (MCV) of Virginia Commonwealth University, presently under the direction of Drs. Mario Aceto and Louis Harris, with E.R. Bowman and E.L. May. The hot-plate assay is carried out at NIH, NIDDK by M. Mattson and A. E. Jacobson.

The various animals and assays which are used are as follows: (1) Studies using rodents: (a) Antinociceptive assays in mice using hot-plate [44] tail flick [45] and phenylquinone [45] procedures; (b) Narcotic antagonist assay in mice, using the tail flick antagonism vs. morphine [45] procedure; (c) Rat continuous infusion procedures (modification of the procedure of Teiger [46]). These include substitution for morphine and, occasionally, a primary physical dependence determination.

(2) Studies in the rhesus monkey. (a) Single dose suppression in morphine withdrawn monkeys (carried out at MCV). (b) Precipitated withdrawal in non-withdrawn monkeys (at MCV). (c) Self-injection in monkeys trained on codeine (at the University of Michigan (UM), under the direction of Dr. Gail D. Winger and, occasionally, at MCV under the direction of Dr. Robert L. Balster). (d) Drug discrimination in monkeys (at UM), under the direction of Dr. Charles P. France. (e) Antinociceptive assay — a new procedure [47] initiated by Dr. Woods (UM) for the study of the antinociceptive effect of opioids in the monkey. (f) Primary physical dependence (carried out both at MCV and UM).

(3) In vitro determination of the binding affinity of opioids by displacement of [^{3}H]etorphine from rat cerebral membrane preparations, and the electrically stimulated mouse vas deferens assay (carried out at UM by Drs. Fedor Medzihradsky and Charles B. Smith, respectively).

Testing for stimulants and depressants

The suggestion presented to the Executive Committee by Dr. James H. Woods (American Psychological Association representative) in 1980 that the CPDD support a screening facility for testing sedative and stimulant drugs for abuse potential was passed in principle that year, and the mechanism for doing so was left to a subcommittee (Drs. Woods, Jacobson, Jaffe, and Schuster).

After several years of preliminary testing of facilities and procedures, the Drug Testing Program of the incorporated Committee was expanded to include stimulants and depressants and, in 1988, the CPDD accepted compounds in the new program submitted from the pharmaceutical industry as well as from international organizations such as the WHO. The initial laboratories involved in the stimulant/depressant group were The University of Chicago, under the direction of Dr. Chris Johanson (succeeded by Dr. William Woolverton in 1987), the Medical College of Virginia with Drs. Louis Harris and Graham Patrick, and The Johns Hopkins University, with Drs. Joseph Brady, Roland Griffiths and Nancy Ator. More recently, the University of Michigan joined this program, under the direction of Dr. Gail Winger. Dr. Edward Cone, in the Intramural Research group at NIDA, initially collaborated in these testing facilities by obtaining solubility and stability data on the drugs. The CPDD presently offers evaluation of compounds in the stimulant or depressant classes using the following methodology.

(1) Initial screening tests, to provide potency estimates and the physical dependence potential of the examined compound, are carried out at the Medical College of Virginia under the direction of Drs. G. Patrick and L. Harris. The procedures include: (a) an assessment of activity in an inverted screen test, and spontaneous locomotor activity in mice; (b) assessment of physical dependence potential by substitution in pentobarbital-dependent rats using continuous intraperitoneal infusion; (c) primary physical dependence determination in rats, by infusion.

(2) Self-administration studies are carried out at the University of Michigan under the direction of Dr. Gail Winger. The reinforcing properties of an intravenously administered drug is determined by self-administration in rhesus monkeys.

(3) Drug discrimination studies are obtained at The University of Chicago under the direction of Dr. W. Woolverton. The discriminative stimulus properties of drugs are determined in rhesus monkeys trained to discriminate pentobarbital or D-amphetamine from saline, through intragastric infusion.

(4) Drug discrimination in baboons by oral administration (under the direction of Drs. Roland Griffiths and Joseph V. Brady, The Johns Hopkins University) is carried out for particular compounds, when necessary.

Human testing

With the loss of the Lexington facilities in 1976, the question of assessment of drugs in humans has been discussed at almost every subsequent CPDD meeting. Dr. D. Jasinski noted, at the CPDD, Inc., Annual Meeting in July, 1977, that he hoped better ways for narcotic evaluation would emerge out of necessity. In July, 1979, a grants program was initiated to improve methodology for clinical screening and to facilitate the evaluation of pharmacological substances with respect to their abuse potential in humans. In December, 1982, Dr. J. Woods presented the case for human studies which would be carried out under CPDD auspices in a manner similar to preclinical studies. A new committee was formed to evaluate the feasibility of this approach. Dr. Charles P. O'Brien, the chairman of this Human Testing Committee in June, 1983, reported on the results of a questionnaire that was sent out to investigators asking whether they would be interested in participating in a human testing program. The feasibility of this approach was questioned by several CPDD members, due to the limited financial resources of the CPDD and a variety of other reasons. Although Dr. Schuster's suggestion at that meeting that the CPDD might serve as a consulting body and endorse particular centers rather than accept funds directly for fee-for-service was not immediately acted on at that time, it was the harbinger of future thinking and decisions on the subject.

At the Interim Meeting in 1983 in San Juan, Dr. Mendelson suggested that the CPDD initiate an action meeting between interested drug firms, federal representatives, and the CPDD Human Testing Committee for exploration of the next step. Dr. O'Brien noted, during the Annual Meeting in St. Louis in 1984, that a number of centers had indicated their interest in human testing (Duke University, University of Pennsylvania, The University of Chicago, The Johns Hopkins University, and Harvard's McLean Hospital). In 1985, at the Interim Meeting in Maui, Dr. Marian Fischman was given the mandate to determine which testing procedures are available for behavioral as well as related metabolic and neurologic-neuroendocrine testing, and the validation of the various procedures. Dr. Loretta Finnegan was asked to concurrently review current attitudes and polices of institutional review boards with respect to including males, females, adolescents and elderly people as test subjects. The Chairman of the Executive Committee, Dr. Kreek, noted that it was important to develop a list of valid tests which could be suggested for use, and a list of where those tests could be performed. Such a document would be an important resource for government, academia

and industry. Dr. Kreek further noted that it would be more plausible for companies to make their arrangements with individual investigators, once an appropriate site was identified, rather than CPDD undertaking the actual testing and acting as an advocate for the drug to the FDA and DEA. Lastly, she noted that CPDD might support the testing of a few, initial, model compounds to validate procedures. At the Interim Meeting in 1986 Dr. Fischman suggested the organization of a conference involving the CPDD, regulatory authorities, the WHO, NIDA and the IFPMA, and a publication reviewing human testing. The objectives of the conference were elaborated by Dr. Fischman at the Interim Meeting in 1987 and included educating participants concerning what human testing can offer, the kinds of data which are collected and the current status of research. This meeting entitled 'Testing for Abuse Liability of Drugs in Humans' was held on November 5–6, 1988, at the Scanticon Conference Center in Princeton, and it was co-chaired by Drs. M. Fischman and N. Mello. The conference was jointly sponsored by the CPDD, NIDA, and the FDA, and it was attended by a group of about 80 individuals representing the various constituencies for which the meeting was conceived. The publication on the conference [47] discussed the history of testing procedures in humans and the current state of the field. Discussion was centered around the conclusions which can be drawn from such testing, and those areas which require further research.

Funds and awards

Two new awards, as well as Travel Fellowships, were instituted during the post-NRC period. In 1981, Dr. Adler suggested the establishment of an award for administrators in the alcohol, drug abuse and mental health fields. Although many awards have been established for scientists, the CPDD felt that individuals who pursued science administration perform a valuable service and should be honored with their own award. This award was named J. Michael Morrison, Jr., in honor of a young, recently deceased administrator at NIDA who represented excellence in science administration. The J. Michael Morrison, Jr., award for outstanding service as an administrator was established as a biennial award, and consists of a plaque and travel expenses to attend the Annual Scientific Meeting of the CPDD. The first such award was given to Dr. Robert Petersen, of the National Institute of Mental Health (ADAMHA), in 1982 (Table XXV lists subsequent awardees).

The second new award, to honor the memory of Dr. Joseph Cochin, a former Executive Committee member, Chairman, and Executive Secretary was established in 1986, and named the J. Cochin Young Investigator Award. The creation of the Cochin award was suggested by Dr. Kornetsky at the 1985 Interim Meeting in Maui. He noted that Dr. Cochin had been very supportive of young investigators and that this award would be a fitting memorial to Dr. Cochin. The first award was given in 1987 to Dr. Michael Bozarth (then at Concordia University, Canada) (Table XXV). The award was established to recognize research contributions in any facet of the field of drug abuse and is given annually to an investigator who has not attained his or her 40th birthday by July 1 in the year of the award. The awardee receives an inscribed plaque and travel expenses to attend the Annual Meeting of the CPDD. Both the Cochin and Morrison awards, as well as the aforementioned Eddy award, are now administered by a separate Awards Committee composed of a number of national and international experts in the field who are not members of the CPDD, as well as a few CPDD members and the contemporary Eddy awardee.

Lastly, in 1983, the CPDD established travel fellowships to attend its annual meeting. As suggested by Dr. Kreek, the CPDD agreed to grant ten such awards (extended to twelve in 1987, including two foreign scientists working in the U.S.) to young researchers who obtained their Ph.D. degree or who have completed their medical residency within the previous five years and give promising evidence of future careers in the scientific areas encompassed by

the CPDD. The initial awards were made for the 1984 Annual Meeting in St. Louis by a subcommittee on grants and fellowships. Dr. Hollister appointed Dr. Mary Jeanne Kreek as Chairman of this subcommittee, with Drs. W. Martin, L. Robins and R. Griffiths. The Travel Award for each grantee was limited to $750 plus waiver of the registration fee for the meeting.

Possible future changes in the Incorporated Committee and conclusion

The broadening scope of the CPDD in response to the national crisis caused by chemical dependence in the 1980s was exemplified by significant changes in organization and structure of the membership, active consideration of conversion to a scientific society to expand membership, and increasingly close relations with NIDA and other governmental agencies. As previously noted, at the Annual Meeting of the CPDD in June, 1988, the members of the Board voted in a manner consistent with a fundamental change in the nature of the CPDD. It was decided to no longer reject the reconstitution as a membership organization, so that the CPDD could continue to increase its responsiveness to the concerns of scientists in the many different fields of research which address drug abuse.

The CPDD had changed incrementally over the 50 years of its existence, slowly at first and then with increasing rapidity during the past twelve years. Initially a small, closed group concerned with a search for a better analgesic, the CPDD has attempted to meet the challenges brought about by the discovery of multiple opioid receptors and their endogenous ligands in human brain and tissue, as well as by the social problems caused by the wide-spread abuse of other psychotropic drugs. Continuity of CPDD activities was ensured through the office of the Executive Secretary of the Corporation, Dr. M. Adler at Temple University, and by providing orderly transitions of leadership of the Chairman-elect, Chairman and Past-chairman as members of the Board. The CPDD plans continuation of two formal meetings of the Board each year, one in conjunction with the annual scientific meeting and an interim meeting in conjunction with the American College of Neuropsychopharmacology. Meetings of the executive working group (or Action Committee), Animal Testing Program, and other committees occur as required during the year.

The recent impact of AIDS in association with parenteral drug abuse, the advent of opioid and amphetamine-like controlled-substance analogs and the epidemic of cocaine abuse have placed new responsibilities on CPDD to serve as a scientific advisory group to government agencies, the pharmaceutical industry, and to scientific and professional organizations affected by drug abuse and chemical dependence. The CPDD has responded by expansion of preclinical and clinical drug-testing programs, by organizing conferences directed at specific drug-related topics, and by increased interactions with NIDA, DEA, FDA, and the WHO. One relatively new area of concern for the CPDD is the abuse of alcohol. Although alcohol is undoubtedly the most widely abused substance in the United States and in many other countries, the CPDD did not begin to include alcohol in its activities until its incorporation in 1976 (although a joint meeting was held with The Committee on Alcohol and Drug Dependence, Council on Mental Health of the AMA in 1969, as noted previously). During the post-NRC period the membership of the Committee has been chosen in part to reflect recognition of the problem. In 1987 the Annual Scientific Meeting in Philadelphia was held as a joint meeting with the Research Society on Alcoholism (RSA) and symposia, such as 'Effects of Alcohol and Drugs on Fetal Development', 'Psychiatric Aspects of Alcohol and Drug Abuse. Drug and Alcohol Interactions', and 'Self-Administration Models in Alcohol and Drug Abuse', were arranged to elucidate contemporary research in the field. Papers from these symposia were published as part of the Proceedings of the 49th Annual Scientific Meeting [48].

At the Interim Meeting in San Juan in December, 1988, a new area of potential interest for the CPDD, the effect of narcotics on the immune system, was broached by Drs. K.C. Rice and A.E. Jacobson. This was stimulated by the accumulating evidence in the scientific literature that opioids affect immune function, and these data were summarized at a recent NIDA Technical Review [49]. An ad hoc committee was appointed by Dr. Dewey, with Dr. Rice as Chairman, to examine the feasibility of testing various opioid receptor agonists and antagonists for their immunosuppressive (or immunostimulant) properties as an expansion of the Drug Testing Program in the 1990s. New challenges, such as those associated with control of drug use in the workplace and perceptions by the public of widespread corruption of the legal system resulting from illegal drug traffic and use, face CPDD as we enter the 1990s. The CPDD can be expected to maintain and expand its vital leadership role in the scientific evaluation of problems resulting from drug abuse and in providing advice concerning responses to those problems.

Acknowledgements

We would like to acknowledge, and thank, Dr. Mary Jeanne Kreek, for it was at her urging that this historical account was undertaken. We express our gratitude to Dr. Clifton K. Himmelsbach and William R. Martin (mentioned frequently in this history) for their helpful discussions, correspondence and reference material. The authors would also like to thank various members of the Committee for their enthusiastic response to this paper and for their many suggestions for its improvement. Special thanks are due to Drs. Martin W. Adler, Joseph V. Brady, Thomas F. Burks, Marian W. Fischman, Charles W. Gorodetzky, Louis S. Harris, and James A. Woods who, with their knowledge of the history of the CPDD gained through close association with the Committee over many years, helped us recall the events of the past several decades and untangle a convoluted history. Heartfelt thanks are due to Sussie Robinson, office-staff member of the Department of Pharmacology and Toxicology, Medical College of Virginia, Virginia Commonwealth University for typing a substantial portion of the manuscript and especially for her patience and dedication in making many revisions.

References

1 N.B. Eddy, The National Research Council Involvement in The Opiate Problem, 1928–1971, National Academy of Sciences, Washington, D.C. 1973.
2 For publications from The Addiction Research Center (Himmelsbach, Isbell, Frazer, Wikler, Andrews, Martin, Gorodetzky, Jasinski, Cone et. al.) see Annotated Bibliography of Papers from The Addiction Research Center, 1935–1975, National Institute on Drug Abuse, U.S. Department of Health, Education and Welfare, Public Health Service, Alcohol, Drug Abuse and Mental Health Administration, DHEW Publication No. (ADM) 77–434, Rockville MD 1978.
3 National Research Council: Report of Committee on Drug Addiction, 1929–1939 and Collected Reprints, 1929–1941. Chemical Pharmacological and Clinical Studies, 1581 pp.
4 L.F. Small and R.E. Lutz, Chemistry of The Opium Alkaloids. Public Health Rep., Suppl. 103 (1932).
5 L.F. Small et al., Studies on Drug Addiction. Public Health Rep., Suppl. 138 (1938).
6 H. Krueger, N.B. Eddy and M. Sumwalt, The Pharmacology of The Opium Alkaloids. The Public Health Rep., Suppl. 165 (2 Vols.) (1942).
7 E.C. Kleiderer et al., Pharmaceutical Activities of the I.G. Farbenindustrie Plant, Hoechst am Main, Office of Publication Board, Department of Commerce, Report No. PB-981, Washington, DC, 1945.
8 J. Weijlard and A.E. Erickson, J. Am. Chem. Soc., 64 (1942) 869; K. Unna, J. Pharmacol. Exp. Ther., 79 (1943) 27.
9 N.B. Eddy, E.L. May and E. Mosettig, J. Org. Chem., 17 (1952) 321.
10 N.B. Eddy, C.F. Touchberry and J.E. Lieberman, J. Pharmacol. Exp. Ther., 98 (1950) 121; See also Appendix 4, pp. 205–209 of Ref. 1.
11 N.B. Eddy and E.L. May. Synthetic Analgesics, Part II-B, 6,7-Benzomorphans, Pergamon Press, London, 1966.
12 S. Archer et al., J. Med. Chem., 7 (1964) 123. See also Appendix 4, pp. 211–215 of Ref. 1.
13 See Appendix 4, pp. 196–201; 245–248; 249–250 of Ref. 1.
14 R.W. Houde, S.L. Wallenstein and A. Rogers, Clin. Pharm. Ther., 1 (1960) 163. See also Appendix 4, pp. 215–220 of Ref. 1.

15 Council on Mental Health (A.M.A.), J. Am. Med. Assoc., 186 (1963) 976; 202 (1967) 209; 218 (1971) 578.
16 See Appendix 4, pp. 209–211; 252; 203–205; 201–203; 245; 269–270 of Ref. 1.
17 See Appendix 4, pp. 196; 205; 211; 248–249 of ref. 1.
18 V.P. Dole and M.E. Nyswander. J. Am. Med. Assoc., 193 (1954) 646; M.E. Nyswander, Hospital Practice, 2 (1967) No. 4.
19 Committee on Problems of Drug Dependence, Bulletin on Narcotics, XXV (1972) 25.
20 M.H. Seevers et al., see Appendix 4, pp. 256–269 of Ref. 1.
21 The Committee on Problems of Drug Dependence, Inc., in: J.V. Brady and S.E. Lucas (Eds.), Testing Drugs for Physical Dependence Potential and Abuse Liability, Natl. Inst. on Drug Abuse Res. Monogr. Ser. 52, U.S. Govt. Print. Off., Washington, DC, 1984.
22 A.E. Jacobson, Biological evaluation of compounds for their physical dependence potential and abuse liability. X. Drug testing program of the Committee on Problems of Drug Dependence, Inc. (1986), in: L.S. Harris (Ed.), Problems of Drug Dependence: 1986, Natl. Inst. on Drug Abuse Res. Monogr. Ser. 76, Washington, D.C., U.S. Govt. Print. Off., 1987, pp. 374–375, and references therein.
23 Consensus document by ASPET and the Committee on Problems of Drug Dependence, The Pharmacologist, 29 (1987) 20.
24 A.E. Jacobson, Biological evaluation of compounds for their physical dependence potential and abuse liability. IX. Drug testing program of the Committee on Problems of Drug Dependence, Inc. (1985), in: L.S. Harris (Ed.), Problems of Drug Dependence: 1985. Natl. Inst. on Drug Abuse Res. Monogr. Ser. 67, Washington, D.C., U.S. Govt. Print. Off., 1986, p. 397.
25 M.D. Aceto, L.S. Harris and E.L. May, Dependence studies of new compounds in the rhesus monkey, rat and mouse (1985), in: L.S. Harris (Ed.), Problems of Drug Dependence: 1985, Natl. Inst. on Drug Abuse Res. Monogr. Ser. 67, Washington, D.C., U.S. Govt. Print. Off., 1986, pp. 399–452.
26 J.H. Woods et al., Evaluation of new compounds for opioid activity (1985), in: L.S. Harris (Ed.), Problems of Drug Dependence: 1985, Natl. Inst. on Drug Abuse Res. Monogr. Ser. 67, Washington, D.C., U.S. Govt. Print. Off., 1986, pp. 453–489.
27 See pp. 372–373 and 387 in Ref. 22.
28 M.D. Aceto, E.R. Bowman, L.S. Harris and E.L. May, Dependence studies of new compounds in the rhesus monkey, rat and mouse (1986), in: L.S. Harris (Ed.), Problems of Drug Dependence: 1986, Natl. Inst. on Drug Abuse Res. Monogr. Ser. 76, Washington, D.C., U.S. Govt. Print. Off., 1987, pp. 392–447.
29 J.H. Woods et al., Evaluation of new compounds for opioid activity: 1986 annual report, in: L.S. Harris (Ed.), Problems of Drug Dependence: 1986, Natl. Inst. on Drug Abuse Res. Monogr. Ser. 76. Washington, D.C., U.S. Govt. Print. Off., 1987, pp. 448–484.
30 A.E. Jacobson, Biological evaluation of compounds for their physical dependence potential and abuse liability. XI. Drug testing program of the Committee on Problems of Drug Dependence, Inc. (1987), in: L.S. Harris (Ed.), Problems of Drug Dependence: 1986, Natl. Inst. on Drug Abuse Res. Monogr. Ser. 81, Washington, D.C., U.S. Govt. Print. Off., 1988, pp. 469, 480–481.
31 M.D. Aceto, E.R. Bowman, L.S. Harris and E.L. May, Dependence studies of new compounds in the rhesus monkey, rat and mouse, 1987, in: L.S. Harris (Ed.), Problems of Drug Dependence: 1987, Natl. Inst. on Drug Abuse Res. Monogr. Ser. 81, Washington, D.C., U.S. Govt. Print. Off., 1988, pp. 485–542.
32 J.H. Woods, F. Medzihradsky, C.B. Smith, G.D. Winger and D.E. Gmerek, Evaluation of new compounds for opioid activity: 1987 annual report, in: L.S. Harris (Ed.), Problems of Drug Dependence: 1987, Natl. Inst. on Drug Abuse Res. Monogr. Ser. 81, Washington, D.C., U.S. Govt. Print. Off., 1988, pp. 543–588.
33 A.E. Jacobson, Biological evaluation of compounds for their dependence liability. XII. Drug testing program of the Committee on Problems of Drug Dependence, Inc. (1988), in: L.S. Harris (Ed.), Problems of Drug Dependence: 1988, Natl. Inst. on Drug Abuse Res. Monogr. Ser., Washington, D.C., U.S. Govt. Print. Off., 1989, pp. 392–420.
34 M.D. Aceto et al., Dependence studies of new compounds in the rhesus monkey, rat and mouse (1988), in: L.S. Harris (Ed.), Problems of Drug Dependence: 1988, Natl. Inst. on Drug Abuse Res. Monogr., Washington, D.C., U.S. Govt. Print. Off., 1989, pp. 468–515.
35 J.H. Woods et al., Evaluation of new compounds for opioid activity, in: L.S. Harris (Ed.), Problems of Drug Dependence: 1988. Natl. Inst. on Drug Abuse Res. Monogr., Washington, D.C., U.S. Govt. Print. Off., 1989, pp. 421–467.
36 Bull. Narc., XXXII (1980) 1–99.
37 Mixed Agonist-Antagonist Analgesics. C.R. Schuster and L.S. Harris (Eds.), Drug Alcohol Depend., Vol. 14 (Special issue) 1985, pp. 221–431.
38 Report of the Committee on Problems of Drug Dependence Consensus Committee, Drug Alcohol Depend., 17 (1986) 279–295.
39 J.H. Woods and C.R. Schuster, Drug Alcohol Depend., 17 (1986) 105–106.
40 Stimulants and Hallucinogens, C.R. Schuster, J.H. Woods and H. Halbach (Eds.), Drug Alcohol Depend., Vol. 17 (Special issue) 1986, pp. 107–278.
41 Drug Dependence: Benefit-Risk Ratio Assessment of Agonist-Antagonist Analgesics, C.E. Johanson and T. Yanagita (Eds.), Drug Alcohol Depend., Vol. 20 (Special issue) 1987, pp. 289–409.
42 H. Isbell, Work of the NIMH Addiction Research Center, Public Health Service Hospital, Lexington, KY, Appendix I, Bull. Drug Addiction and Narcotics, National Academy of Sciences-National Research Council, Publ., 1954, pp. 840–852; see also L. Lasagna

and H.K. Beecher, Studies and Speculations on the Antagonism of Morphine by Nalorphine (N-Allylnormorphine) in Man, ibid, Appendix J, pp. 873–889.
43 G.A. Deneau and M.H. Seevers, Bull. Drug Addict. Narc., Natl. Acad. Sci.-Natl., Res. Council Publ., Addendum 2, (1962) 1–26.
44 L. Atwell and A.E. Jacobson, Lab. Animal, 7 (1978) 42.
45 W.L. Dewey et al., J. Pharmacol. Exp. Ther., 175 (1970) 435; W.L. Dewey and L.S. Harris, J. Pharmacol. Exp. Ther., 179 (1971) 652.
46 L.A. Dykstra and J.H. Woods, J. Pharmacol. Methods, 15 (1985) 263.
47 Testing for Abuse Liability of Drugs in Humans, in: M. Fischman and N. Mello (Eds.), Natl. Inst. on Drug Abuse Res. Monogr., Washington, D.C., U.S. Govt. Print. Off., 1989, in press.
48 Problems of Drug Dependence: 1987, in L.S. Harris (Ed.), Natl. Inst. on Drug Abuse Res. Monogr. Ser. 81, Washington, D.C., U.S. Govt. Print. Off., 1988.
49 Natl. Inst. on Drug Abuse, Tech. Rev., 1988.