U.S. – Netherlands Addiction Workshop and Binational Symposium on Drug Abuse, Addiction Research and Innovation

October 19-20, 1999

Netherlands Research and Development Program on Substance Use and Addiction
U.S. National Institute on Drug Abuse

PREFACE

With the Exchange of Letters at this workshop and symposium, the National Institute on Drug Abuse (NIDA) and our Dutch colleagues initiated a program of collaboration and cooperation on biomedical and behavioral research on drug abuse and drug-related health issues. I am sure it will prove beneficial to both nations, and am encouraged by the researchers' prompt efforts to exchange information and begin scientific cooperation. This agreement represents another advance in NIDA efforts to foster communication and collaboration between American scientists and our colleagues in other countries. These cooperative agreements allow us not only to develop international research collaborations, but also to build relationships with leaders in other countries. I was pleased to participate in the meeting and look forward to the results of our efforts.

Alan I. Leshner, Ph.D.
Director National Institute on Drug Abuse

The meeting was about international collaboration, kindled by the belief that combining efforts in stimulating research on addiction will have great potential. The Exchange of Letters gives substance to this belief, and the addiction research as well as the efforts to improve addiction care and prevention will undoubtedly benefit from it. The document is special in that it allows for various ways of collaboration in addition to just traveling of scientists. Its flexible format is much appreciated. The document is of high relevance for the Dutch Addiction Program that is supported by our two organizations. The contributions by the speakers and their audience provided excellent opportunities to pinpoint topics for collaboration that will have added value with respect to ongoing research activities in our two countries. With great expectations we look forward to the research activities that will follow from this meeting and the cooperative agreement.

Prof. dr. Eduard C. Klasen
Director Council for Medical Science Netherlands Organization for Scientific Research/NWO

Drs. Henk J. Smid
Director Health Research and Development Council/ZON

ACKNOWLEDGMENTS

The Netherlands Research Program on Substance Use and Addiction wishes to thank all the people and organizations that helped to develop the binational Exchange of Letters and the meeting that marked the start of what will most certainly be a stimulating cooperation between NIDA and the Program. The stimulating and excellent input from both the American and Dutch participants of the meeting confirmed our ideas that further collaboration will broaden and deepen our understanding of addiction, its treatment and the ways to prevent it.

This first inspiring step in US-Dutch cooperation would not have been possible without the support, encouragement, assistance and advice from the many individuals and institutions which we all owe our gratitude. Especially we wish to thank the Dutch Minister of Health, Welfare and Sport and her Ministry (including its Attaché and Staff at the Dutch Embassy in Washington D.C. and its Department of Addiction Care), our hosting organizations ZON and NWO and our collaborative centers the Trimbos-institute, the Amsterdam Institute on Addiction Research and the Royal Netherlands Academy of Arts and Sciences. Last but most certainly not least, we thank our colleagues at NIDA of whom we got so much help, support and understanding.

Dr. G.H.M.M. ten Horn, chair
Prof. dr. J.M. van Ree, vice chair
Netherlands Research Program on Substance Use and Addiction

The NIDA International Program gratefully acknowledges the support, advice, encouragement, and assistance of the individuals and institutions whose contributions helped develop the binational Exchange of Letters and the program for this inaugural meeting between American and Dutch researchers. Through their stimulating exchange of ideas and thoughtful assessment of research issues, the presenters and speakers provided an excellent framework for the development of productive binational collaborations. Special thanks go to the U.S. Department of State, the staff of the Dutch Embassy in Washington, D.C., and my colleagues in The Netherlands.

M. Patricia Needle, Ph.D.
Director, International Program
Office of Science Policy and Communications
National Institute on Drug Abuse

EXECUTIVE SUMMARY

During a two-day meeting in Amsterdam, the national organizations responsible for drug addiction research in the United States and The Netherlands signed documents agreeing to promote collaboration in biomedical and behavioral research on drug abuse and drug-related health issues. The formal Exchange of Letters was signed by Alan I. Leshner, NIDA Director; Henk J. Smid, The Netherlands Health Research and Development Council (ZON); and Eduard Klasen, The Netherlands Organization for Scientific Research (NWO) during October 1999 ceremonies at the Royal Netherlands Academy of Arts and Sciences. The two nations agreed to cooperate by exchanging information and materials about drug addiction research, support exchange visits by scientists, and hold joint symposia to promote collaborative research efforts.

Exchange efforts began immediately, as a small group of researchers from both countries discussed an agenda for future research cooperation between NIDA and the Dutch agencies during the U.S. – Netherlands Addiction Workshop, chaired by Dr. Leshner and Dr. Jan M.van Ree, Rudolf Magnus Institute for Neurosciences, Utrecht. The following day, approximately 100 Dutch researchers, policymakers, and healthcare providers joined the addiction workshop participants to review current research and areas for potential collaboration at the Binational Symposium on Drug Abuse, Addiction Research, and Innovation, which was organized by NIDA and the Netherlands Research and Development Program on Substance Use and Addiction (Programma Verslaving) in cooperation with the Amsterdam Institute of Addiction Research and The Netherlands National Institute of Mental Health and Addiction (Trimbos-institute).

Eduard Klasen, Alan I. Lesner, Henk J. Smid.

Kathleen Merikangas, Terry Robinson, Wim van den Brink.

Addiction Workshop

On the first day, during the addiction workshop, Dr. Smid, Dr. Klasen, and Dr. M. Patricia Needle, International Program Director, NIDA Office of Science Policy and Communications, presented the two nations' aims for the collaborative agreement and ways to stimulate binational cooperation among researchers. Five speakers introduced possible areas for cooperation: Dr. Kathleen Merikangas, Yale University, focused on risk, resiliency, and vulnerability; Dr. Henk Rigter, Trimbos-institute, examined addiction prevention; Dr. Terry Robinson, University of Michigan, Ann Arbor, reviewed multidisciplinary research on relapse and craving; Dr. Wim van den Brink, University of Amsterdam, discussed drug abuse treatment; and Dr. Claire Sterk, Emory University, Atlanta, addressed monitoring drug use and accessing hard-to-reach populations.

Following the general session, participants met in small groups to discuss each topic, reviewing ongoing research efforts in both countries and identifying promising areas of potential collaboration.

At the end of the workshop the chairs Dr. Van Ree and Dr. Leshner concluded that the binational collaboration offers unique opportunities to implement prevention and treatment programs in different cultural contexts. Attention could be given to the abuse of benzodiazepines and other prescription drugs. Four areas of common research interest were noticed: validation of outcome measures; the impact of anxiety, depression and stress on prevention and relapse; human and animal research on relapse, including treatment options combining pharmacotherapy and behavioral therapy; and drug use patterns in relation to the environment and individual characteristics of drug users.

Alan I. Lesner, Jan M. van Ree.

Binational Symposium

On the second day, participants in the Binational Symposium focused on four research topics: (1) pathways to addiction, (2) prevention, (3) drug abuse treatment and relapse prevention, and (4) monitoring illicit drug use. Presenters included Dr. C. Hendricks Brown, University of South Florida, Tampa; Dr. Mirjam Gerrits, Rudolf Magnus Institute for Neurosciences, Utrecht; Dr. Stephen T. Higgins, University of Vermont, Burlington; Dr. Klasen; Dr. Leshner; Dr. Merikangas; Dr. Needle; Dr. Richard Rawson, University of California, Los Angeles; Dr. Rigter; Dr. Robinson; Dr. Gerard M. Schippers, University of Amsterdam Medical Center; Dr. Ton Schoffelmeer, Free University, Amsterdam; Dr. Smid; Dr. Sterk; and Dr. Van den Brink.

Speakers discussed research into pathways of addiction, including studies about the progression from experimental drug use to addiction; risk factors such as genetic vulnerability, gender, stress, depression, anxiety, and pre- and postnatal exposure; expectancies models; and integrating animal models with human models. Researchers also explored those factors that protect individuals from progressing to addiction. In the sessions on prevention research, speakers reported on the research-based principles of effective prevention developed through NIDA-supported research as well as on ways to develop and target prevention interventions, increase and measure their effectiveness, and conduct randomized prevention trials. Participants were enthusiastic about the U.S. development of an international registry to list ongoing prevention trials. Discussing drug abuse treatment and relapse prevention, speakers addressed behavioral and pharmacotherapy treatment models; the biomedical and behavioral bases of drug-seeking behaviors; the use of neuroimaging techniques in treatment research; and the need to develop or expand multidisciplinary research, longitudinal studies, outcome measures, clinical treatment trials, and drug abuse treatment for individuals with comorbid psychiatric and somatic diagnoses. Participants also reviewed the effective approaches to addiction treatment identified by 30 years of NIDA-supported scientific research and clinical practice, which are presented in the newly published Principles of Drug Addiction Treatment: A Research-Based Guide. Addressing efforts to monitor illicit drug use, participants discussed

techniques to conduct basic epidemiological research, focusing on accessing hard-to-reach populations, female drug users, and new drug users; network-based outreach efforts; and ways to predict developments in drug use patterns. Speakers also explored the impact culture, policy, rituals, and market dynamics can have on drug use patterns.

Following formal presentations that reviewed the state of the science in the four discussion areas, participants met in small groups to identify research similarities, differences, and priorities for both countries. They suggested that future priorities include efforts to validate prevention and treatment outcome measures and called for expanded efforts to integrate animal and human models and for additional research on topics such as relapse, craving, risk factors, benzodiazepine addiction, cognitive psychology, expectancies models, treatment options that combine behavioral therapies with pharmacotherapy, and environmental and individual patterns that contribute to drug use and addiction.

M. Patricia Needle,Richard Rawson, C. Hendricks Brown.

NEXT STEPS

After two days the researchers concluded that collaboration could create unique opportunities to improve understanding of drug use and addiction as well as prevention and treatment of drug abuse. Collaborative research on both sides of the Atlantic has serious potential for significant, innovative, quality research with additional value for both countries.

It seems appropriate to build a network to exchange ideas. This network would be helpful in creating a research agenda including bridging animal and human research and validating outcome measures for prevention and treatment research, including the effectiveness and efficacy of prevention and treatment programs.

Participants recommended combining U.S. and Dutch research on important future themes. An important area that was identified was relapse, both in biomedical and behavioral research. The theme could be the umbrella for several studies on the role of genes and brain structures, expectancy factors, and combined pharmacological and behavioral treatment programs. Another important area would be new vulnerability factors for addiction such as stress, anxiety, and depression. Combined research would also create unique possibilities to understand the effects of prevention and treatment programs by transporting them to another local context. Furthermore, it would help to join forces on new issues such as addiction to prescription drugs (e.g. benzodiazepines) and the harmfulness of MDMA (ecstasy).

The four major themes that were discussed were biomedical, behavioral and social scientific research on becoming addicted (risk, resiliency and vulnerability factors), prevention addiction (effectiveness of preventive interventions models), treating addiction (combining pharmaco-therapy with behavioral models), preventing relapse (multidisciplinary research of relapse and craving) and monitoring of illicit drug use (including reaching difficult-to-reach groups).

Future research on risk, resiliency and vulnerability should bridge the gap between animal and human research (e.g., prenatal drug exposure and postnatal maternal deprivation). Serious risk factors for addiction such as stress, anxiety, and depression, could be the themes for combined biomedical and behavioral research. Special efforts should be made to elaborate expectancy models.

In the area of future prevention research, participants recommended emphasizing combinations of preventive interventions in community-based trials. Binational experiments to validate outcome measures would help to develop powerful tools for testing preventive

interventions and could also form the basis for international registration of prevention trials. Effective prevention outcomes could be linked with biological markers.

The research agenda for treatment and relapse prevention could include fundamental research on combined pharmacotherapy and behavioral treatment, effectiveness studies of behavioral treatment models, and long term treatment and follow up studies on the pharmacological aspect of craving and relapse prevention. The agenda could also include efficacy studies, implementation of evidence-based treatment, and research on combinations of addiction and other psychiatric disorders. There is also a great need for improved instruments to measure treatment outcomes. Neuroimaging techniques would certainly add to the success of addiction research. Furthermore, research on medications to treat cocaine addiction should continue.

Qualitative research on drug use is necessary to disclose patterns of drug use among difficult-to-reach groups such as homeless people and ethnic minorities. Monitoring studies could include cultural aspects and rituals of drug use among these groups. Participants added that research should also focus on female users.

The two-day gathering of researchers proved to be a good basis for generating ideas for binational studies on addiction and drug use. It was concluded that such meetings should take place on a regular basis in both countries.

U.S. – NETHERLANDS ADDICTION WORKSHOP

International Research Issues

Dr. Needle described efforts by NIDA to build collaboration in international drug abuse research. She provided participants with a brief outline of funding and training opportunities for international researchers supported by NIDA and the National Institutes of Health (see Appendix B). Dr. Needle added that Dutch and U.S. researchers should have a good understanding of the drug abuse epidemic in both countries and excellent communication to ensure successful collaborations. She said it is essential for collaborators to understand the U.S. National Institutes of Health guidelines for research involving human subjects, especially Institutional Review Boards (IRBs). IRBs are established at the local level to ensure that research risks are reasonable in relationship to anticipated benefits, ensure that subjects are selected equitably, monitor the informed consent process, minimize risks to subjects, and maintain the rights and welfare of subjects. U.S. funding agencies require IRB approval for all research involving human subjects, whether the research is conducted in the United States or another country, including international collaborations supported by administrative supplements to existing NIDA grants, domestic grants with foreign components, and foreign grants. The IRB approval process can be lengthy, in part because IRB members are all volunteers. The Department of Health and Human Services Office of Human Research Protection (OHRP) oversees implementation of the regulations governing IRBs and develops assurances between investigators and NIH on compliance with guidelines on protecting human subjects in research. OHRP provides education, instruction, liaison, and coordination activities through its Web site at http://ohrp.osophs.dhhs.gov

The Dutch Addiction Program Collaborating with NIDA

Dr. Klasen recalls to memory the start of the Decade of the Brain in the USA and the Dutch counterpart Brainwork 2002. In The Netherlands one of the outcomes of the increased attention for the brain, was the initiative to start a nationally coordinated and supported program, integrating research on addiction for the biomedical, behavioral and social sciences, including epidemiological and health care research. In addition to research, the program aims for innovation of addiction care and prevention. Regarding a topic such as addiction, scientific knowledge should not be isolated from the struggle to gain control over its incidence, over its debilitating consequences and over its often chronic and insidious effects. In other words fundamental research should in this particular area have a direct connection with innovation of prevention and treatment. It is for this reason that the Dutch Addiction Program is supported by both the Health Research and Development Council (ZON) and The Netherlands Organization for Scientific Research (NWO).

The handling of drugs is evidently a major challenge to both countries. One way to increase opportunities to gain control over the phenomena, abuse and addiction, is to reach a better insight into its causes, its manifestations and its consequences. Scientific research is, without any doubt essential in acquiring this necessary knowledge. The fact that American and Dutch scientists are joining forces to improve our knowledge on the phenomena of drug addiction is considered an extremely meaningful event. The document undersigned by the three organizations involved, has in many ways potential to bring together research from both sides of the Atlantic in various forms. Creating opportunities is a first necessary step, scientists should next designate areas and research themes that, as a result of combining forces, will prove to be a mutual asset.

Risk, Resiliency, and Vulnerability

Moderator Dr. Van den Brink stressed the need to expand research into psychological factors that increase vulnerability to drug abuse. Expectancies models seem to be pretty important in predicting alcohol use, abuse, and, possibly, dependence, but these models are not often used in drug abuse research. Cultural expectancies might be different for different drugs in different countries; for example, attitudes toward cannabis and cocaine probably differ between the United States and The Netherlands. Participants suggested that research target younger adolescents rather than college students, use a developmental approach with prospective studies, and integrate expectancies models with biological parameters as alcohol researchers have done. Another area for potential collaboration would be family aggregation studies to identify risk factors. Three demographic factors make it easier to conduct family aggregation studies in The Netherlands: very low mobility, relatively intact family structures, and relatively dense population centers. Participants suggested that other studies focus on high-risk factors and the differences and similarities among drug use, drug abuse, and drug dependence.

The group also discussed the links between animal and human research models, focusing on the need to improve the validity of animal models so that they can be more easily adapted to human clinical trials. This is of particular importance for human and animal research on prenatal and postnatal exposure to nicotine, alcohol, cocaine, or other drugs and on the impact of postnatal and early maternal deprivation on addiction. Participants urged that a binational data base list researchers' contact information and grant activities, and that U.S. and Dutch scientists collaborate at U.S. primate centers to conduct research on the neural mechanisms and cognitive behavioral aspects of addiction.

Addiction Prevention

Moderator Dr. Brown stressed that research must be conducted on measure validation. One trial currently underway in The Netherlands is based on the Good Behavior Game, which was developed in the United States with support from NIDA. The classroom-based intervention was designed to track early aggression and its relationship to later drug use. The Dutch trial involves 650 children from 13 different schools in a fully randomized trial, and could be expanded to include measures for anxiety and depression and biological markers for stress like cortisol. U.S. researchers will benefit from the lower attrition rates and higher response rates in The Netherlands; Dutch researchers benefit from the long-term, complementary funding; and both countries benefit from the research findings if mechanisms are discovered to prevent drug use among aggressive children. Participants also discussed a Dutch study on prevention of depression that is being conducted by the Trimbos-institute with support from ZON. Five hundred 15- to 16-year-olds who have been diagnosed with moderate levels of depression are taking part in randomized intervention trials. Researchers will examine the relationship among depression, anxiety, and drug use or abuse. The participants suggested expanding the scope of the study to a full epidemiological sample with long-term follow-up.

Several opportunities for binational collaboration were identified, including disseminating empirically proven programs in effective ways to new communities, expanding effectiveness and multi-site trials, implementing NIDA-supported school- and family-based programs in The Netherlands, adapting life skills programs used in the United States for The Netherlands, and conducting research on drug abuse risk predictors. Participants strongly recommended that a NIDA registry of preventive trials be expanded to include international research. Another key area would be evaluation studies to examine the impact of interventions. Finally, participants suggested that international groups convene to discuss innovations in research on specific drugs, especially Ecstasy, methamphetamine, and cocaine.

Relapse and Craving

Moderator Dr. Robinson led the discussion of animal models. Participants concluded that animal models do not capture the richness and complexity of all the variables that contribute to addiction in humans, especially polydrug use and length of drug use. A more complex variation in patterns of drug pretreatment regimens is required if researchers are to successfully examine relapse through animal models. For example, it is not clear whether the kinds of neurobiological or behavioral changes that occur following relatively short exposure to repeated, intermittent drug administration are the same or fundamentally different from those elicited by escalating binge models. Also, pathways to relapse and craving

vary under different human conditions, but animal models provide very little knowledge about either the range of stimuli available in the real world or the neurobiological pathways in which different stimuli lead to relapse and craving. Conversely, animal models have provided essential details about brain function that expanded scientific knowledge about human learning and memory and contributed to research in cognitive psychology. Drug abuse research that is based on animal models may successfully expand our knowledge of the neurobiological impact of drugs. Participants urged that more research be conducted on sophisticated imaging studies, on the neurobiological subsystems that provoke relapse in reinstatement models, on the transitional states between drug use and drug abuse; and on the interaction among craving, the subjective experience of desire, and relapse to determine if treating craving would prevent relapse.

Drug Abuse Treatment

Moderator Dr. Rawson recommended that researchers conduct comparative longitudinal studies using existing data sets, focusing on the patterns of treatment participation that have developed in the United States and The Netherlands as a result of the two countries' very different cultures and policies toward treatment. Chronological comparisons could investigate how the natural history of drug abuse is changed by the treatment system and how different treatment systems affect other health care costs. Participants also discussed ways to improve the Addiction Severity Index (ASI) and develop treatment outcome measures. Areas of potential collaboration include a Dutch project attempting to operationally define and measure treatments as they are delivered, cocaine use, implementing the NIDA-developed treatment protocol manuals in existing Dutch trials, Dutch research on benzodiazepine abuse treatments, and polydrug use.

Monitoring Drug Use

Moderator Dirk J. Korf suggested that collaborative research on monitoring drug use and accessing difficult-to-reach populations concentrate on female drug users and drug dealers and their networks, in particular from a more perspective that not a priori defines women as victims, but as active actors instead (for example female recreational drug use). Participants also discussed research on new drug users, including the definition of a new user, and new use patterns. Researchers could address factors that make a drug popular in one subculture but not others; the evolution of use patterns; mechanisms to predict developments in drug use from one culture to another; and the impact of culture, policy, and rituals on drug use.

Plenary Session Commentary

Dr. Van Ree, who co-chaired the session with Dr. Leshner, identified four areas of common research interests:

- Validation of prevention and treatment outcome measures
- The impact of anxiety, depression, and stress on both prevention and relapse
- Relapse, especially research on craving, expectations, cognitive psychology, treatment options that combine pharmacotherapy and behavioral therapy, benzodiazepines, and polydrug use, and
- Drug use patterns in relationship to the environment (setting, market dynamics, and policies) and individual characteristics of drug users.

Dr. Leshner asked participants to consider unique opportunities offered through U.S. and Dutch collaboration, particularly implementing prevention and treatment programs in different cultural contexts and the true impact of different cultures on drug abuse, prevention, and treatment. He added that more research is needed on abuse of benzodiazepines and other types of prescription drugs.

BINATIONAL SYMPOSIUM ON DRUG ABUSE AND ADDICTION RESEARCH AND INNOVATION

Opening Speech

Dr. Els Borst-Eilers, Dutch Minister of Health, Welfare and Sport

100 years ago the United States conquered the Philippines and was then confronted with the opium problem. The Bishop of the Philippines, Charles H. Brent, emerged as the American leader of the anti-opium movement and gave this movement the character of a moral crusade. He can also be regarded as the leader of the international anti-opium movement. In 1909, on the initiative of the United States, the first international meeting of the Opium Commission was held in Shanghai. In retrospect, this meeting appears to have opened the way for extensive regulation of drug production and drug trading.
Both humanitarian and economic considerations lay behind the steps that the United States took then, on a world stage still very much dominated by colonial relationships. The Netherlands itself was one of those colonial powers at the time, and at first it objected strongly to the American plans.

Today, a century later, the world has certainly changed greatly, but sensitivities still exist between our two countries on the subject of drug policy.

But today I do not want to go more deeply into those political sensitivities. I am delighted to be able to open a conference whose focus is on the areas where we agree. These areas of agreement can be found in the field of addiction research. Yesterday the United States and the Netherlands signed an agreement to collaborate in this research. I am glad, because it is always better to approach this issue from the viewpoint of the common elements than from that of the differences. I am convinced that the effectiveness and efficiency of addiction policy, prevention and care stands or falls with the input it receives from experiments, model projects and other scientific research. I strongly support evidence-base policy wherever possible.

Today I want to contribute to your discussion by suggesting three points to consider in your research policy. The first point relates to the use and harmfulness of stimulants. From a scientific point of view, it is interesting to investigate the exact nature of that harmfulness, and whether the harmfulness of these substances is commensurate with their status in the eyes of the law – legal or illegal – and with specific policy interventions. This is an area in which there are substantial differences between our countries. Cannabis policy is one example, and so is the fact that policy on tobacco and alcohol is considerably stricter in the United States than it is here.

In my view, a balanced and comprehensive approach to harmful stimulants is an important principle. In the Netherlands we are now moving towards a more integrated policy stance on stimulants, in which the harmfulness of a substance is more important than its legal aspects. Scientific research is an indispensable source for policy development according to this view.

A second point to consider is research into the effectiveness of treatments. In the Netherlands we invest relatively heavily in an easily accessible and differentiated aid program. However, we still know comparatively little about the effectiveness of the different therapeutic interventions. I understand that the United States also needs this knowledge urgently. We must join forces in this area, too. In the Netherlands we not only value research into ways of improving existing treatments, but also innovation. For example, think of the study on the use of heroin as a remedy for chronic opiate addiction, and the study on coming off drugs under sedation.

A third point to consider is monitoring of developments and trends in the use of illegal drugs and other stimulants. To get a clear picture of all relevant developments, I have set up the National Drug Monitor (NDM). The NDM's reports will be at the service of both domestic users and international agencies. I expect much from exchanges of expertise and joint research in the area of monitoring, too.

Connections and contacts have long existed between scientific researchers on both sides of the Atlantic, and scientists speak a universal language. That is why it is natural that the first formal agreement between the Netherlands and the United States about the addiction problem should relate to scientific collaboration. I expect much from this collaboration, given the first-class reputation of the NIDA and the substantial sums that the institute invests in addiction research. Conversely, the Netherlands' policy, care and scientific research can suggest interesting approaches for American researchers. The present addiction program is the first joint research program between the two intermediate research organizations, the Netherlands Organization for Scientific Research and for fundamental research and the Health Research and Development Council of the Netherlands for practice-oriented research.

This approach has proved successful, and is now leading to closer collaboration between the two organizations in other fields of research and in the area of housing. It is of course crucial for the research findings to be unambiguous and usable. They must be relevant to the issues about which governments, welfare agencies, social workers, patients and citizens are concerned. Both ordinary citizens and the people and organizations that determine policy must benefit from the new insights, whether in the form of more specific information about the harmfulness of a particular illegal drug, or of the relative effectiveness of particular treatments.

Therefore, I am pleased to inform you that I have decided to extend my financial commitment to the Netherlands Research and Development Program on Substance Use and Addiction by three years.

I wish you all much success in the collaboration between our two countries. I hope that this collaboration will help to promote a constructive dialogue and yield scientific findings that will support a balanced and effective policy on addiction and stimulants.

Drug Abuse Research in the New Millennium: Challenges and Opportunities

Alan I. Leshner

Advances in science are providing us with unprecedented opportunities to develop new approaches for treating and preventing drug abuse and addiction, and for dealing with the myriad of effects that accompany drug abuse.

As the premier research institution in the United States responsible for biomedical and sociobehavioral research on drug abuse, the National Institute on Drug Abuse's mission is twofold: (1) to conduct and support research on drug abuse across a range of disciplines, and (2) to ensure rapid and effective dissemination and use of this research to improve prevention, treatment, and policy. NIDA supports more than 85 percent of the world's research on drug use, abuse, and addiction — including an active and growing portfolio of binational and multinational research.

NIDA is continuously working to replace ideology with science. There is a unique disconnect between public perceptions about drug abuse and addiction and the scientific reality documented by research. The fact is, advances in science have revolutionized our fundamental views about drug abuse and addiction, demonstrating that drug abuse is a preventable behavior and that drug addiction is a treatable brain disease with significant social and behavioral aspects. From our behavioral science portfolio we have found that people take drugs for two major reasons: to feel good and to feel better when they are not feeling good. But we need to better understand why and how people become addicted — why individuals compulsively seek and use drugs despite their knowledge and understanding of drugs' negative consequences.

Technological improvements in neuroscience now allow us to observe and verify our assumptions about the effects of drugs on the brain. Through neuroimaging technologies such as positron emission tomography, we know that prolonged drug use actually changes the brain in fundamental and long-lasting ways. Improving understanding of these changes in brain function is a key to explaining the phenomenon of addiction.

In addition to supporting studies that help us better understand the mechanisms of addiction, NIDA drug abuse research priorities in the new millennium include:
(1) responding to emerging drug epidemics such as methamphetamine, (2) gaining a better understanding of the addictive properties of nicotine, (3) identifying risk and protective factors in prevention, (4) understanding and preventing relapse, (5) developing more effective behavioral therapies and medications, and (6) launching and expanding the National Drug Abuse Treatment Clinical Trials Network.

A number of epidemiologic monitoring sources have documented the rapid increase in methamphetamine abuse in the U.S. NIDA is intensifying efforts to investigate the mechanisms and consequences of methamphetamine addiction and to support development of effective prevention programs and treatment medications. NIDA is also continuing to support research into nicotine addiction, which in turn contributes to our basic understanding of the neurobiology of addiction, long-term neurological consequences, and effective prevention interventions and treatments. Toward this end, the NIDA Intramural Research Program has launched an adolescent nicotine addiction clinic to focus on this important issue.

The next generation of prevention research at NIDA is heavily emphasizing protective and resiliency factors. The goal is not just to better understand what makes people more or less vulnerable to addiction, but also to examine what factors protect individuals from becoming drug users. As always, disseminating research findings and translating them into practice for prevention and treatment will continue to be a critical component of NIDA research.

Another significant research area for NIDA is investigating what causes relapse, which is a critical issue in the treatment of drug abuse. Scientific research has shown that relapse can be triggered by a variety of factors including stress, drug-associated stimuli, and low doses of drugs of abuse. The new NIDA publication, Principles of Drug Addiction Treatment, discusses relapse and other important areas of treatment research. It provides a variety of effective approaches to drug addiction treatment that were developed through three decades of scientific research and clinical practice. For example, it presents the scientific data to support the fact that drug addiction is a chronic disease that can be treated as effectively as other chronic illnesses. Indeed, data on drug addiction treatment compliance and relapse rates are comparable to those for diabetes, hypertension, and asthma. Drug users in treatment are as compliant as anyone else. Principles of Drug Addiction Treatment documents that the most effective treatment is comprehensive and addresses the biological, behavioral, and social aspects of drug addiction. For example, most successful treatment programs use a treatment plan that proceeds from initial assessment to provide both core services (behavioral therapy, counseling, pharmacotherapy, clinical and case management, substance use monitoring, self-help or peer support groups, and continuing care) as well as ancillary services (child care, family counseling, housing, transportation, financial, legal, HIV/AIDS, education, medical, mental health, and vocational services). In an effort to disseminate research findings in a useable format to practitioners, NIDA has also begun issuing a series of practical manuals to guide science-based drug treatment programs; the first two manuals provide models for treating cocaine addiction.

NIDA is committed to developing effective treatments to combat addictions. NIDA supported research has already contributed to the development of a number of pharmacological and behavioral approaches to treat addiction, such as methadone, LAAM, and buprenorphine for opiate addiction; and a variety of treatments for nicotine addiction, including the nicotine patch, gum and spray. Although no medications have yet been identified to treat cocaine addiction, current studies have identified some promising compounds. To promote the development of effective behavioral therapies and medications that can be used in diverse patient populations, NIDA recently launched its National Drug Abuse Treatment Clinical Trials Network, based on the National Institutes of Health model for cancer treatment clinical trials. The National Drug Abuse Treatment Clinical Trials Network joins university- or hospital-based research centers with community-based treatment programs to test potential drug abuse behavioral therapies or medications in real-life settings with diverse populations from different geographical areas.

NIDA's comprehensive research portfolio and our commitment to disseminate and share research findings with our international colleagues will be useful as we all work together to combat drug abuse and addition.

Risk, Resiliency, and Vulnerability: Individual differences in susceptibility to substance dependence

Mirjam Gerrits

A critical factor in the initiation of drug dependence is the individual susceptibility for the dependence creating properties of abused drugs. An experimental animal model with predictive value for the dependence creating properties of psychoactive substances, i.e. drug self-administration, can be used to delineate factors relevant for the individual susceptibility for initiation of substance dependence.

The available data indicate a role for endogenous opioids and opioid receptors in the initiation of cocaine self-administration behavior. That is, treatment with the mu opioid receptor antagonists naltrexone, an opioid antagonist, decreased the cocaine intake but only when a threshold dose of cocaine was offered. In fact, naltrexone caused a rightward shift in the dose response curve for cocaine intake, indicating that the animals were less

sensitive for cocaine reward after opioid blockade. This effect was also present when naltrexone was administered in the ventral tegmental area (VTA), the cell body region of the mesocorticolimbic dopamine system, but not when administered in dopaminergic target regions. Recent studies have demonstrated an involvement in the opioid receptor system in the sensitivity for the reinforcing effects of drugs of abuse. Thus, opioid systems, in particular those in the VTA, may play a role in the individual sensitivity for addictive drugs during the development of substance dependence, and therefore in the individual proneness to become addicted.

In other experiments the effect of individual experiences on initiation of drug self-administration has been studied. For example, prenatal exposure to psychoactive drugs significantly affects the initiation of drug self-administration. Rats born from females treated with morphine during gestation exhibited higher heroin and cocaine intake during initiation of self-administration. Another factor that seems to be of significance to the initiation of drug self-administration is stress. Emotional stress, as opposed to physical stress, enhanced the initiation of cocaine and morphine intake in drug-naive animals. These results indicate that individual experiences pre- and postnatally affect the initiation of drug-self administration, and hence, the development of substance dependence.

Taken together, the results of our previous studies indicate that individual experiences are important risk factors in the development of substance dependence and that the opioid systems, in particularly in the VTA, may be an important neurochemical substrate in this respect.

Principles of Effective Prevention

The U.S. Experience

C. Hendricks Brown

Prevention research has been dominated by approaches that first demonstrate which programs are effective in preventing drug abuse, followed by efforts to identify the key components of those effective programs. A NIDA publication, Preventing Drug Use Among Children and Adolescents: A Research-Based Guide, is a compendium of findings from NIDA-supported prevention research. Twenty years of prevention research in the United States has generated substantial evidence about interventions that successfully reduce drug use and abuse. But success rates vary for interventions implemented in different communities and at different times. By understanding these variations, researchers may be better able to identify the most effective components in a prevention program.

U.S. prevention interventions fall into three general categories: indicated, selective, and universal. Indicated interventions identify high-risk individuals and provide specific interventions to address the individual's vulnerabilities. Selective interventions identify a group of people at-risk for drug abuse, such as children of addicted parents, and provide interventions that address the group's shared vulnerabilities. Universal interventions address a range of vulnerabilities that might exist within a community; even though they are aimed at the full population, they often appear to have strong impact on the highest risk children. All of these approaches have empirical evidence that shows demonstrable impact on preventing or delaying the onset of drug use.

There are clear indications that for interventions to be successful, they need to take into account the context in which the intervention is delivered. Contextual factors in the classroom, school, or community often account for a high degree of intervention effect. Thus changes in the multiple environments of a child have more potential than interventions aimed at the child alone. Furthermore, there is evidence that interventions that pull together deviant adolescent peers often produce more drug use and problem behavior than control settings. This finding has implications for the design of indicated interventions.

Prevention of Substance Use and Abuse: The Practice in the Netherlands from a Binational Perspective

Henk Rigter

Prevention of drug use and abuse is high on the political and policy agenda in the Netherlands. Nevertheless, prevention research is lagging behind the standard set in the United States. The ZON/NWO program may provide the resources needed to establish the long-term commitments and the scientific infrastructure that are essential to further develop this line of research.

The present-day U.S. classification of prevention interventions (indicated, selective (or targeted), and universal) has been adopted in the Netherlands as well. The former distinction between primary, secondary, and tertiary prevention is loosing support. The bad news is that most of the many prevention interventions in the Netherlands are not proven to be efficacious, let alone to be effective. The good news is that in each of the three categories (indicated, selective, universal) there are quite a number of interventions in the Netherlands that are similar to interventions carried out in the U.S. So, there are ample opportunities for binational comparisons.

The Netherlands has had a leading role in developing indicated prevention interventions. Examples include programs for syringe exchange, methadone maintenance, and prevention

of overdose. There is relatively good evidence to believe that these interventions are effective. The policy context in which these indicated interventions are delivered in the Netherlands differs from that in the U.S., allowing for stimulating comparisons.

An example of selective prevention interventions are approaches targeted at families at risk of getting problems with drug use. One goal of these interventions may be to help parents to raise their children in such a way that they resist using drugs. The evidence in favor of such interventions is not yet convincing, but NIDA has funded promising projects such as the Strengthening Families Program. This is an area where binational collaboration may be difficult to achieve. There are cultural differences in family life between our two countries. This may not be true of other selective interventions, such as those targeted at truants or school drop-outs, or at adolescents with legal problems.

Examples of universal prevention interventions in the Netherlands include mass-medial-campaigns, school-based programs, and community interventions. Concurrently, mass-medialcampaigns focusing on cannabis are running in the U.S. and in the Netherlands. It is hard to compare the outcomes of these efforts. For one, the mass media in the U.S. are dissimilar to those in the Netherlands. Yet, we could learn from each other's experiences. In particular, we are interested in the Netherlands to learn about the 'ingredients' that are essential for mass-medial campaigns not just in ensuring information seeking but also in producing behavioral change.

As for school-based interventions, the Dutch Trimbos-institute runs the 'Healthy School' project. Its origins date back more than ten years ago, and more than half of all high schools in the Netherlands (plus some elementary schools) have adopted this project. The 'Healthy School' project has been selected by the European Commission as an exemplary approach for the other Member States. The project has been evaluated repeatedly, with positive outcomes. We are aware of U.S., NIDA sponsored, findings that the effectiveness of school-based interventions can be further improved by embedding these approaches in a community context, like in project STAR. School-based interventions have a transient effect, and mass medial campaigns in themselves are not very instrumental in producing behavioral change. Together, the sum (of the effects of interventions) may be more than the parts. It may be essential to include these interventions in a community approach. The community approach needs to be designed learning from U.S. experiences. There is a world to win here, in binational collaboration.

Relapse and the Role of Craving

Reinstatement of Drug-Seeking Behavior in Rats is Associated with Drug Hyperresponsiveness

Ton Schoffelmeer, Louk Vanderschuren and Taco de Vries

Drugs of abuse such as psychostimulants, opiates, nicotine and alcohol acutely enhance the activity of the mesolimbic dopamine system, which is thought to play a crucial role in their motivational effects. Recent studies in our laboratory showed that intermittent exposure to these drugs causes a long-lasting increase in the reactivity of dopaminergic nerve terminals in the rat nucleus accumbens towards depolarization. Moreover, this long-term increase in the responsiveness of mesolimbic dopamine neurons appeared to be associated with sensitization of drug-induced psychomotor activity. Studying the effects of a series of direct and indirect dopamine receptor agonists on non-reinforced drug-seeking behavior long after extinction of intravenous heroin and cocaine self-administration, we found that only those drugs that caused a sensitized psychomotor response in psychostimulant or opiate exposed rats induced a robust reinstatement of cocaine- or heroin-seeking behavior. These and other data suggest that hyperresponsiveness of motivational systems in the brain may play an important role in the persistence of an addiction prone state and relapse to drug taking long after detoxification. Accordingly, readjustment of the persistent neuroadaptations that underlie hyperresponsiveness of the mesolimbic system may represent an effective strategy for the clinical management of drug addiction.

Pharmacological and Psychological Bases of Craving

Terry Robinson

Drug use changes brain function in ways that are fundamental and long-lasting, if not permanent. This is clearly evident in the phenomenon of psychomotor sensitization, which refers to a progressive increase in the psychomotor effects of drugs with repeated use. An animal that has been exposed to drugs of abuse, but abstinent for months to years, often exhibits a dramatic hypersensitivity effect in a drug challenge. This sensitization is seen following the administration of a number of drugs, including cocaine, morphine, ethanol, and nicotine. Psychomotor stimulant effects and reward response rates are similarly affected by previous drug exposure. In association with behavioral sensitization researchers have documented enhanced dopaminergic responsivity long after discontinuation of use for amphetamine, cocaine, morphine, nicotine, and alcohol, as well as structural changes in brain reward circuitry. Thus, drug use also results in a variety of persisting biochemical adaptations involved in motivation and reward that may contribute to craving and relapse. Furthermore, these neurobiological adaptations are not the inevitable consequence of drug exposure, but are powerfully modulated by the environmental context in which the drug is

given. Future research could focus on integrating animal and human models in multidisciplinary studies; transitional states between drug use and abuse; and the relationship between craving, the subjective experience of desire, and relapse.

The Role of Pharmacotherapies in Addiction Treatment (Biomedical Research)

Drug Abuse Treatment: The Dutch Situation and Themes for Collaboration

Wim van den Brink

The scientific literature provides the Dutch researcher with a relatively clear picture of the American drug use and drug abuse treatment situation. The epidemiological and treatment situation of The Netherlands, however, is less well-documented and not so easily accessible to American researchers. The Dutch treatment system uses a two-dimensional model of treatment goals (abstinence versus risk reduction) and treatment settings (voluntary versus compulsory), which affects patient outcomes. Dr. Van den Brink reviewed current drug abuse research efforts, describing randomized clinical trials, naturalistic studies, target population studies, and a new treatment initiative called 'To Score Results' launched by collaborating addiction treatment centers in The Netherlands.

Based on similarities and differences between the United States and The Netherlands, he identified several areas for potential collaboration: (1) identification and comparison of the treatments provided to addicted populations in treatment, (2) identification and comparison of the treatments and outcomes for subpopulations of drug addicts, (3) development and testing of clinically relevant outcome parameters for use in future studies, (4) systematic exchange of knowledge on newly developed compounds for drug treatment, and (5) participation of both countries in multi-center effect studies in order to increase generalizability. The first two themes could be studied through the expansion of the U.S. program, Drug Evaluation Network System (DENS), to The Netherlands. DENS is currently used in 5 pilot cities covering 30 treatment programs and will cover 50 of the largest U.S. cities in the near future (Kleber, McLellan, Carise, 1998). DENS is an ongoing nationwide electronic information system that continuously monitors the characteristics of patients who enter drug abuse treatment and treatment protocols using the Addiction Severity Index (ASI) and the Addiction Program Inventory (API), respectively. Extension of DENS to The Netherlands could provide insights into the similarities and differences between the two treatment systems and could be used for benchmark studies between the two treatment systems.

Drug Abuse Pharmacotherapy in the United States

Richard Rawson

The United States has taken a very active role in developing a range of pharmacotherapies for the treatment of addictions (primarily opiate pharmacotherapies such as methadone, LAAM, buprenorphine, and naltrexone), delivering these medications under circumstances optimal for rehabilitation, and using optimal doses of new and conventional medications. During the more than 30 years since methadone maintenance treatment was approved by the U.S. Food and Drug Administration, researchers have documented the effectiveness of methadone and LAAM in suppressing withdrawal symptoms, diminishing craving, reducing illicit drug use, and promoting normal psychosocial function. Long-term studies have found that, when compared with heroin users, patients in agonist pharmacotherapies live longer, experience improved quality of life, and are less likely to test positive for HIV or other infectious diseases. Other research documents the cost-effectiveness of methadone maintenance treatment by comparing the costs of treatment with the costs of incarceration.

With the eagerly anticipated approval of buprenorphine/naloxone (Bup/Nx) for treatment of opiate dependence, patients and clinicians will have a valuable new option. Patients whose illicit opiate use is eliminated by daily Bup/Nx will have the choice of moving on to treatment with naltrexone administered 3 times per week, or no medication. If a withdrawal strategy is unsuccessful or not appropriate, patients will, in most cases, have the option of maintenance treatment with LAAM or methadone. Multisite trials of Bup/Nx are underway in the United States. Dutch researchers and clinicians expressed great interest in expanding this work to include Dutch sites. Researchers from the United States and The Netherlands expressed great interest in developing effective pharmacotherapies for other abused drugs, such as cocaine and methamphetamine.

Of particular interest to the Dutch participants was the development of treatments for benzodiazepine abuse and dependence. Participants from the United States and The Netherlands expressed the belief that the abuse of benzodiazepines is a hidden problem. Many of the individuals who abuse benzodiazepines are outside the substance abuse treatment system; thus, little attention has been given to devising and evaluating treatment protocols for this patient group. A cooperative effort to develop a common treatment protocol for benzodiazepine abuse and dependence that could be tested in a bilateral trial was enthusiastically discussed.

The Role of Behavioral Models in Addiction Treatment (Behavioral Research)

Improving Cocaine Abstinence During Outpatient Treatment and One Year of Follow-up with CRA Plus Contingent Vouchers

Stephen T. Higgins

During the past 10 years our group has been assessing the efficacy of an outpatient behavioral treatment for cocaine dependence that integrates the Community Reinforcement Approach (CRA) with contingency management. A therapist manual describing how to implement this treatment is available free from NIDA (Budney & Higgins, 1998, NIDA Therapy Manuals for Addiction, Manual 2, NIH Pub. # 98-4309.) The efficacy of this treatment has been supported in four controlled clinical trials conducted in our clinic (Higgins et al., 1991, 1993, 1994, 2000). My presentation briefly describes prior trials, but mostly focuses on a recent clinical trial that assessed whether contingent incentives reinforce cocaine abstinence in dependent outpatients (N=70), and whether that effect is sustained during one year of follow-up (Higgins et al., 2000). All patients met DSM III-R criteria for cocaine dependence and received 24 weeks of treatment and one year of follow-up assessments. The treatment provided to all patients combined counseling based on the CRA with incentives in the form of vouchers exchangeable for retail items during treatment weeks 1 through 12 and state lottery tickets during weeks 13 through 24. In one (contingent group) of two groups, incentives were delivered contingent on cocaine-free urinalysis results, while in the other group (non-contingent group) incentives were delivered independent of urinalysis results. In addition to urinalysis monitoring during treatment, drug use and related areas of functioning were assessed at intake and 6, 9, 12, 15, and 18 months after treatment entry. Significantly more patients in the contingent group than the noncontingent group achieved 12 weeks of continuous cocaine abstinence during treatment ($p<0.05$); and point prevalence cocaine abstinence during the one-year follow-up period was significantly greater in the contingent group than the noncontingent group ($p<0.05$). CRA plus contingent incentives can directly reinforce sustained cocaine abstinence in dependent outpatients, and this effect remains discernible during the year after treatment termination.

The Role of Behavior Models in Addiction Treatment

Gerard M. Schippers

Research on behavioral models needs a good breeding ground. The Netherlands offer some favorable conditions for that. The typical attitude towards addicted people is relatively accepting in accordance with the general tolerant attitude towards deviancy and social weakness. This attitude has had consequences for drug abuse treatment. The treatment system is less ideologically driven and less dependent on ex addicts. It ranges from abstinence oriented therapeutic communities, to over the counter methadone, users rooms and heroin prescription (thus far only in a randomized control clinical trial). There is some backlog in research, however. Now the Dutch system wants to adopt the results on evidence based treatments leading to a series of research projects supporting implementation of new treatment methods.

Behavior-oriented research in the Netherlands can be presented under the subheadings: cognitive processes research, motivation, treatment methods and the treatment process.

Cognitive processes

Studies should be mentioned on the role of cognitive processes in conditioned opiate craving and relapse. Research groups in the Hague, in Amsterdam, and Nijmegen have been working on fundamental questions and models. Next to the University of Nijmegen Research Group on Addictive Behaviors (UNRAB), other groups (University of Maastricht) have started research into the psychological mechanisms, and factors like mood and expectancies, on cue reactivity and the effects of alcohol. Research on the expectancies about alcohol is a second group of studies worth mentioning. Valid Dutch Expectancy Scales have been developed (University of Maastricht). UNRAB added a thus far underreported aspect of the expectancies on alcohol outcomes, namely the symbolic expectancies, referring to the nonpsychotropic, mainly social meanings that alcohol (and drug) taking can have.

Motivation

Some studies contribute to a better understanding of the Transtheoretical Model of Change, originated by Prochaska and DiClemente. A group of the University of Maastricht has stressed the role of self-efficacy in health behavior change and contributed to the development of the Health Action Process Approach, originated by Schwarzer in the US. Another line of research in motivation is more qualitative. It tries to enlighten the motivational structure of addictive behaviors, where motivational ambivalence seems to be one of the key concepts. It is reflected in the terms ‘readiness to change’, ‘decision balance’, ‘goal seeking’ and ‘resistance’. All these concepts seem to refer to a divided self. Several instruments have been designed to measure these ambivalences. In the U.S. instruments like the Motivational Structure Questionnaire, based on the current concern approach by Klinger and colleagues is developed by Miles Cox (now at Bangor, Wales, U.K.). This closely resembles the work of a group in the Netherlands (UNRAB) which has developed a theory of personality called the Dialogical Self. The Self-Confrontation Method, which originated from this theory has just started to be applied to addicted people both in the Netherlands as by people from Yale.

Treatment

Eight clinical trials are now ongoing in the Netherlands, testing behavioral treatment in the addictions.

1 Dialectical Behavior Therapy for substance abusing patients with a borderline personality disorder (AIAR-Amsterdam)
2 Cue-exposure therapy for opiate addicts (PRAD – The Hague).
3 CBT for alcoholics with co-morbid anxiety disorders (AIAR/VU Amsterdam)
4 Motivational enhancement and CBT in combination with acamprosate (AIAR Amsterdam)
5 Motivational enhancement and the Drinker's Check Up in the Internal Medicine ward of a General Hospital (AIAR – Amsterdam)
6 Motivational Enhancement for substance abusers with and without cognitive handicaps (University of Groningen – dept. Clinical Psychology).
7 CBT Partner therapy for substance abusers in combination with acamprosate (University of Amsterdam/AIAR).
8 (Ultra) rapid detoxification and the Community Reinforcement Approach (NOVADIC-St. Oedenrode/VU Amsterdam)

Monitoring Illicit Drug Use and Reaching Difficult-to-Reach Groups

Monitoring Drug Abuse Trends in Difficult-to-Reach Populations

Claire Sterk

In the United States, efforts to monitor trends in drug use and abuse can focus on gathering incidence and prevalence data from the general population; targeted surveys of institutions, such as emergency rooms, drug treatment centers, prison or jails, and other health or social service delivery sites; and community-based monitoring through local surveys, key informant interviews, in depth interviews, observations, and mapping.

Monitoring efforts must consider such variables as local circumstances, local subgroups, stage of drug use, polydrug use, and variations in the way drugs are used. Community Epidemiology Work Groups, comprised of community-based interdisciplinary teams of researchers, monitor drug use trends in 20 U.S. cities or regions. Other communities use the RARE approach, or Rapid Assessment, Response, and Evaluation, which builds collaboration among local officials, public health leaders, community leaders, and researchers to provide strategies to enhance prevention efforts, maximize community support and service networks, and provide access to care for the most vulnerable populations. It is important to define the targeted community, whether it is a group of individuals who use drugs together, a city block, a region, or a country.

Difficult-to-reach populations are the least visible but most vulnerable segments of society. U.S. researchers have documented the effectiveness of accessing difficult-to-reach populations through drug treatment centers and other clinical or social service settings, drug courts or prisons, and community-based outreach programs. Outreach-based programs have been shown to reduce drug use and increase access to treatment or needle exchange programs. Network-based outreach programs can focus on dyads; personal/egocentric networks that follow the direct ties between an index person all of his or her network members; and sociometric networks that follow the direct and indirect ties between groups of people. The network-based approach has been shown to be effective in accessing difficult-to-reach populations through longitudinal studies and randomized controlled trials of standard versus network-based outreach.

Monitoring Illicit Drug Use and Difficult-to-Reach Populations in the Netherlands: The Origin of Monitoring Methodologies

Dirk J. Korf

Since the mid 1980s a substantial number of individual studies have been conducted in the Netherlands among hard-to-reach populations of drug users (street addicts, street prostitutes, drug tourists, ethnic minority groups, homeless youth, non-deviant cocaine users, MDMA (Ecstasy)-users, etc.) and occasionally among drug dealers as well. Although some of these studies included a follow-up design and some others were conducted in several regions, none were explicitly defined as monitoring studies. Peter Cohen, who then was the coordinator of the Amsterdam Drug Research Program, played an important role in many of these studies. Snowball sampling was the key methodology in many of these studies, in particular a specific technique (randomized chain referral) developed by Dr. Korf to improve the statistical representativeness of snowball samples. In addition a number of 'cohort studies' on HIV and AIDS were done among predominantly captive samples of heroin addicts, in particular in Amsterdam but in other cities as well. Many of these studies were conducted by a research group supervised by Roel Coutinho (Municipal Health Service Amsterdam). In general these studies were quantitative and many were defined as monitoring studies.

Originally under the supervision of Charles Kaplan, who was 'addiction professor' at the Erasmus University, a number of ethnographic studies were done among non-captive addicts in Rotterdam. Community fieldwork was the methodological keyword here. In recent years the IVO-Institute in Rotterdam, now led by Henk Garretsen, has developed the community fieldwork approach into a more systematic monitoring system (DMS = Drug Monitoring System). Today the original qualitative approach is combined with quantitative methodologies. Though in practice the focus remains on the traditional opiate addicts (and today cocaine and crack cocaine addicts), DMS studies users of 'new drugs' such as MDMA (Ecstasy) as well.

In the early 1990s a research group at the University of Amsterdam supervised by Dr. Korf developed and implemented a monitoring system (Antenna) in collaboration with the Prevention Department of the Jellinek Centre. This monitoring system focuses on new developments in drug use among youth and young adults. The key instrument is a qualitative panel study: insider experts (drug dealers, drug users, DJ's, etc. in the drug scene are interviewed twice a year on developments in drug use in their social networks. In addition surveys are done among 'populations at risks' (such as clubbers and ravers) and among high school students. Antenna also includes some other indicators (e.g. quality of MDMA (Ecstasy), telephone help line statistics).

The National Drug Monitor (NDM)

Although both DMS- and Antenna-methodologies continue to be applied in the cities of origin (Rotterdam and Amsterdam respectively), they play an increasingly important role in other cities and regions in the Netherlands. Elements of both models have been incorporated into the newly developed National Drug Monitor (NDM), which in a way serves as an umbrella for local monitoring studies. The NDM is not restricted to difficult-to-reach populations and includes general population and student surveys and other quantitative methodologies as well.

New research priorities

During the conference, ideas for qualitative research among difficult-to-reach populations have been discussed in an expert group. Proposals should not only focus on qualitative methodologies and on difficult to reach populations, they also should – in the context of cross national studies – have added value and they should be applicable in the two countries (US and the Netherlands). It was concluded that three issues (in random order) would meet the criteria set.

1 **Gender.** Studies in women drug users have traditionally focused on the most visible and socially deprived sub-populations, street prostitutes in particular. As a consequence, the theoretical orientation was dominated by women as victims (i.e. Rosenbaum's 'narrowing perspectives'). More recent models and empirical findings have brought about wider theoretical perspectives that allow the study and understanding of women as more active actors, in particular regarding 'recreational' drug use. Such studies should focus on gender specific drug use patterns and on the role of women in social networks of drug users.

2 **New use and new users.** For quite a long time, new patterns of use and 'new' drugs were believed to be introduced in the Netherlands – and in Western Europe on the whole – after they had become popular in the United States. Often this was defined as 'Americanization' of the illicit drug market. A more critical and evidence based orientation shows that (a) this development is not always empirically true and (b) the interpretation is far too simple.

A scientifically more sound approach would be to study new patterns of use (i.e. the increase of oral application of drugs such as crack cocaine and heroin) and new users (i.e. migrants) from a cross cultural perspective. Which developments in the United States and the Netherlands are converging, which are diverging, and how can this be understood from the context of market dynamics?

3 **Culture, policy and rituals.** Levels and patterns of drug use are often explained from the policy context. Pros and cons of national drug policies are stressed and findings are often interpreted in terms of preferred drug policy, even if cross-cultural differences can not only or only marginally be explained by national drug policies. Moreover, such an approach bares the risk of being blind for cross-cultural similarities that exist despite different drug policies. In order to allow scientific interpretations of effects of drug policy, such effects should be studied empirically. (Two examples. De jure criminalization is not by definition the same as de facto criminalization. Social inclusion and exclusion require proper definition and empirical operationalization.) Avoiding political bias requires genuine interest in general (cross-cultural) social processes. In this respect, the fundamental study of drug use – such as: the process of becoming, being, staying and quitting being a drug user – should be one of the priorities in Dutch-American qualitative drug research.

Workshop I: Risk, Resiliency, and Vulnerability

Relapse and the Role of Craving: Neurobiology of Enhanced Vulnerability to Drug-Seeking Behavior

Taco de Vries

An intriguing issue in addiction research is the high individual variability in the vulnerability to drug abuse. Since similar variation in response to drugs of abuse is observed in laboratory animals, intrinsic biological factors seem to represent a major cause. Theoretical models propose at least two explanations for this phenomenon, i.e. (1) a pre-existing pathology or predisposition, often characterized by an extreme 'need' for novelty, or (2) an induction of long-lasting neuroadaptive changes in the brain by previous contact with drugs of abuse. By combining behavioral, neurochemical, and innovative molecular biological techniques, we aim to unravel the pre-existing neurobiological markers (at the neurochemical and molecular level) of enhanced vulnerability to drug-seeking behavior in central mesolimbic neurons. Secondly, we are interested whether common biological factors underlie both an enhanced vulnerability to develop drug-seeking behavior as well as the incentive-sensitization to drugs of abuse and hyperresponsivity to stress and environmental cues presumed to cause relapse in detoxified individuals. In addition, we will explore the possibility to detect biological markers of enhanced vulnerability in peripheral tissue, as was recently established in blood cells obtained from children of alcoholics (collaboration with J. Ratsma and W.B. Gunning, AMC, Amsterdam).

Psychological Factors Related to Vulnerability

Reinout Wiers

Dr. Reinout Wiers noted that quite a number of vulnerability factors are already known from literature (behavioral impulsivity, conduct disorder, particular neuropsychological measures, peers and parent-child interaction, etc.). His research is focused on the contribution of expectancies regarding the addictive substance. In his view this is a proximal predictor of becoming and staying addicted and may even be a central mediator of other vulnerability factors. Expectancies result from a variety of factors including family history, pharmacological effects of the substance, metabolic sensitivity, peer pressure, etc.
He illustrated his approach by presenting data regarding positive and negative expectancies for high and for low doses of alcohol. Usually, people only look at positive expectancies for low doses and negative expectancies for high doses. The other two alternatives were included in the study by Wiers and showed very interesting correlations with, for instance, family history and age of the subject. This approach appears to have potential in developing and refining treatment and prevention strategies. The model as such also merits further research into the underlying mechanisms at the level of cognitive processes (e.g. conscious versus unconscious expectancies), but may also be included in animal research to get a grip on the physiological underpinnings and to improve the validity of such models. The expectancy approach could be extended to other addictive substances, such as tobacco.

Workshop II: Principles of Effective Prevention

Mass-medial campaigns, schoolbased interventions and community interventions

Henk Rigter

Prevention efforts should be targeted using findings from epidemiological studies and monitoring projects. The National Drug Monitor (NDM), established in the Netherlands in 1999 and run with key support from the Trimbos-institute, presents such findings in annual reports for national and international (European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), Lisbon; World Health Organisation; United Nations) bodies.

The drug most used in the Netherlands, but less than in the United States, is cannabis. According to a recent survey among 22,000 Dutch of twelve years and older, close to 16 per cent have ever used cannabis, and 2.5 per cent in the last month before the interview. Use is highest among youngsters, fading off beyond the age of 30. What does this mean for prevention?

One way to go would be to focus on groups at risk of developing problems with cannabis use. For instance, one may think of truants and school drop-outs (selective intervention). Or we could adopt another approach, targeted at all users of the drug, or at all users-to-be. This is a universal approach, which assumes that there is a relation between total use in a population and the frequency of problematic use. In practice, both approaches are being combined, but yet without evidence of the effect of the constituent or combined ingredients.

There are three main types of universal prevention, i.e., mass-medial campaigns, school-based interventions and community interventions. Recently, two mass-medial campaigns focused on cannabis have been carried out in the Netherlands: one targeted at parents, one at adolescents. In the latter one, a puppet named Stoney became popular. Stoney appealed to the sense of humor of young people. The Stoney campaign was supported by information materials that people were free to take from libraries and post offices. A very large number of leaflets were taken home. Apparently, the campaign fulfilled a need for information. The remaining challenge is how to bring about behavioral change. In conducting mass-medial campaigns, one should specify the desired outcome beforehand. It is unlikely that such a campaign can effect behavioral change, unless such an intervention is embedded in a more encompassing approach.

A second type of universal intervention are school-based programs. The prime example in the Netherlands is the long-standing and successful 'Healthy School' project. The lessons learned from evaluations of this project reveal that educating pupils about drugs and drug use through the curriculum is in itself not very effective, unless combined with training in coping abilities (e.g., resistance to peer pressure), and involvement of parents and school officials in information transfer and the setting up of school policy.

The third type of universal intervention pertain to the community. We know from U.S. studies that the effectiveness of school-based approaches can be increased by embedding these interventions in a broader community oriented framework. This latter step is still lacking in the Netherlands and here is where we may benefit most from binational collaboration.

What we need, in the United States and the Netherlands, is the systematic and tailor-made design of integrated packages of prevention interventions including mass-medial campaigns, and school-based and community-based interventions. In order to achieve that, one needs to focus on the daily life of people in the target group, e.g., adolescents. The Trimbos-institute is carrying out a national program, together with prevention departments of Addiction Care Institutions, entitled: Going Out & Drugs. Its goal is to design and implement prevention interventions targeting the three main domains in the lives of young people: home, school, and recreation. These interventions are meant to expose youngsters and their parents to mutually reinforcing information and other interventions at the major places frequented by them in their daily environment. The effectiveness of this challenging approach will be assessed in the near future.

In addition to data on drug use in general, we need to gather data on the use of each drug separately. A prevention intervention appropriate for drug X may be inappropriate for drug Y. In the Netherlands, we have a nationally representative market (pill testing) monitor specific for MDMA (Ecstasy)-like compounds, including amphetamines. This monitor (DIMS) also serves as a model for the emerging European Early Warning System. DIMS allows us to quickly trace the marketing of (more) unsafe, and even life-threatening substances, and to launch national warning campaigns (ten times so far). By following this approach, excessively dangerous products such as atropine, strychnine, GHB and other substances, have been forced from the market within days. DIMS does not encourage the use of MDMA (Ecstasy) and similar substances. In contrast, leaflets and other information materials warning about ill-effects of the consumption of these substances are actively disseminated through DIMS.

The lessons learned from prevention research in the Netherlands so far include:

1 State the goal of your intervention and the target group to be addressed beforehand.
2 Involve representatives of the target group in designing the intervention(s).
3 The intervention should be a long-lasting investment.
4 Combine interventions (mass-medial, school- and community-based) in order to improve the effectiveness of the approach.

Summery of the presentations of C. Hendriks Brown, Pim Cuijpers and Alfons Crijnen and of the discussion

Wilma Vollebergh

Presentation of C. Hendricks Brown

Dr. Brown concentrates on the U.S.-research on effective prevention. The focus of NIDA is currently on implementation/dissemination of research results and on research on conditions for effective prevention, including epidemiological research on the conditions for the effectiveness of the risk and resilience factors. The two Dutch introductions concentrate on the Dutch situation and its strong orientation towards U.S.-research.
Pim Cuijpers gives an overview of prevention programs in the Netherlands. One third of the 354 programs are school based and ten percent aim at training of professionals. The rest is a variety of approaches. There is little attention for ethnic minorities and family programs.

Presentation of Pim Cuijpers

The effectiveness of the existing programs seems to be low. Only the school based programs could be called effective, although the effects are limited. The community interventions seem to be less effective. Through combination and expansion of the existing interventions, Dr. Cuijpers hopes to improve the effectiveness. Priorities are:

- improvement of the school based programs through measuring the effects of combination of universal, selective and indicated interventions at the same time.
- community intervention trials and trials aiming at families.
- further development within addiction prevention with principles of prevention from the mental health sector.
- dissemination of research results.

Presentation of Alfons Crijnen

Alfons Crijnen concentrates on possibilities and risks for researchers in the context of binational comparison of drug abuse and drug addiction. The conditions for effective binational comparisons are:

- prevalence studies of the (illicit) use of drugs, alcohol and smoking in both countries
- studies on the prevalence and causal mechanisms in terms of risk and protective factors in both countries
- studies on effectiveness and efficacy of preventive interventions in schools, in communities and for parents and peers
- studies on the effectiveness and efficacy of combinations of preventive interventions: combinations of universal, selective and indicated interventions; interventions aiming at dominant risk factors in the different development stages
- dissemination of research results in both countries

The theoretical model for the development of large trials Dr. Crijnen is studying shows that the influence of the family, the school and friends/peers develops over time. ADHD is the dominant behavioral risk factor in the early childhood, expanding with oppositional defiance in the ages between six and eleven. Behavioral problems of children from twelve years of age on manifest most times in conduct disorder (12-18 years) and antisocial personality (18 and older). Dr. Crijnen concludes with a presentation of a nationwide trial on schools and with parents of children in the ages between six and fourteen. The school interventions under research for the youngest is the Good Behavior Game and for the oldest is the Healthy School.

Discussion

- In both the United States and The Netherlands a tendency toward science based prevention is visible. NIDA tests the effectiveness of prevention programs that have been developed and used already to identify promising interventions. Trimbos-institute has a similar function.
- The research programs that are thus developed create a tension between the organizations that organize the interventions and those that research the interventions. The researchers are only willing to give support to the organizers after the research has been done, which is not always possible due to urgent problems.
- The intervention developers sometimes fear that the researchers will claim the right to implement the intervention after the research. The fear can be prevented by agreement at the start of the project.

There have been more studies on cost-effectiveness of interventions in the United States than in the Netherlands where prevention research has not yet developed enough.

Workshop III: Relapse and the Role of Craving

State of affairs and key questions

Vincent M. Hendriks

Focus on the craving component

Relapse can be quite easily defined in operational terms as the full resumption of drug-seeking and drug-administration behavior after a period of (voluntary) abstinence. This definition emphasizes the distinction between a single or temporary lapse, i.e. a single drink/drug intake or a period of controlled drinking/drug use after a period of abstinence as opposed to a full-blown relapse, which involves the reinstatement of addictive behavior.

Craving is much more difficult to define and there are many different conceptualizations of the term. In the (human) addiction field, most definitions of craving converge on the idea that craving is a subjective-motivational desire to experience the effects of a previously used psychoactive substance. However, the conceptualizations of craving diverge with respect to very basic elements; including the following:

1 Which incentive mechanism(s) drive craving?
   - Is craving directed toward the relief of (often conditioned) withdrawal symptoms (negative reinforcement), and/or
   - Is craving directed toward the earlier experienced (and hence often conditioned) pleasurable, positive, or – more in general – incentive properties of a drug (positive reinforcement).

2 When does craving occur?
   - Can craving occur during a period of active drug use, or
   - Is craving exclusively the result of an interruption of 'highly automatized and ste reotyped' (Tiffany) drug use behavior, which occurs, for example, when the drug is not available or when the individual actively makes an attempt to stop his drug use.

3 What is the dimensionality of craving?
   - Does craving constitute a continuum of desire, ranging from normal to intense desire, or
   - Should the term 'craving' be reserved for intense or perhaps even pathological desire? And if so:

4 What constitutes this 'intense subjective-motivational desire'?
   - Does this desire constitute 'intense or excessive wanting' (Robbinson & Berridge), and/or
   - Intense liking?

These are very basic questions about the concept of craving, which need to be clarified in future research. Based on the literature in the field of both animal and human addiction studies, as well as clinical and field observations of active addicts and ex-addicts, some provisional answers emerge:

Ad.1. Craving seems to be predominantly directed toward the appetitive incentive properties of the drug. Arguments in favor of this view include:
- Individuals (humans and animals) will self-administer drugs in the absence of withdrawal symptoms;
- Reinstatement of drug use is easily established in animals and humans even after a long period of abstinence (i.e., long after withdrawal symptoms have faded);
- Many opiate addicts do not report withdrawal symptoms when exposed to drug-associated stimuli;
- Exposure to typical and strong withdrawal-associated stimuli, such as a formerly visited detoxification clinic, does not provoke drug use or relapse into drug use. In general, studies indicate a lack of correlation between withdrawal distress and drug-seeking behavior.

Ad.2. Craving does not merely occur after interruption of 'automatic and stereotyped' drug use behaviors. It is nevertheless more likely to occur in these situations. Arguments in favor of this view include:
- Craving is reported during active drug use periods, during which the drug is readily available and the individual does not attempt to stop;
- In some observational studies, subjectively experienced craving is even reported to increase during or immediately following drug (e.g. cocaine) use;
- Subjectively, the majority of relapsed addicts (hence: in a period that the automatic processes have been interrupted) do not report craving as a primary reason for their relapse;

Ad.3. The term craving should be reserved for intensive desire, parallel to the common use of the term in daily life. Nevertheless, within this right end of the continuum, there are likely to be differences in intensity, ranging from strong desire to extreme desire.

Ad.4. The distinction between a 'wanting' and a 'liking' component within the concept of positive reinforcement is very interesting, and should be explored further in future studies. The 'wanting' component seems to be predominant in craving and seems to become more dominant as the addiction process progresses. However, after long periods of drug use, 'liking' may still occur:
- Field observations indicate that even chronic drug users after many years of use still report an anticipation of liking and indeed a (strong) pleasurable effect after drug intake;
- It may very well be that the balance between 'wanting' and 'liking' in chronic drug users is partly determined by contextual cues. Liking may still occur in a positive context (either internally or externally).

Focus on the relapse component

From many studies and clinical observations, it is well established that

- Addiction is a chronic relapsing disorder with high relapse-rates in both treated and otherwise abstinent addicts;
- Relapse is more common among recently abstinent drug users than among long-time abstinent users. Studies indicate that approximately two-thirds of the relapses occur within three months following treatment;
- Relapse in formerly dependent drug users is common across all types of drugs and follows a similar temporal pattern.

Animal and human studies indicate the following three major types of triggers for relapse:

1 Taking the drug itself (in human studies: a lapse; in animal studies: priming);
2 Exposure to external drug-associated stimuli (e.g. smell, sight location, paraphernalia);
3 Experience of emotional stress (e.g. anxiety).

For each of these types of triggers of relapse, some underlying mechanisms have been identified, which include the following:

Ad.1. Taking the drug itself. In many studies, a priming dose (animals) or lapse (humans) has been demonstrated to easily and rapidly reinstate the old addictive behavior (relapse). Some underlying mechanisms include:

- A priming dose (and drugs in general) activates mechanisms associated with the attribution of increased incentive value to the drug;
- In the field of neurobiology, many studies suggest an important role of dopaminergic systems in the attribution of incentive properties to a stimulus (e.g. a drug). For example, administration of a dopamine antagonist has been demonstrated in animal studies to prevent priming for amphetamines;
- Studies have demonstrated that the mesolimbic dopaminergic system (and perhaps also other neurotransmitter systems) becomes increasingly sensitized by repeated drug administrations, resulting in an increased ability of drugs to produce incentive value. The implication of such sensitization is that ex-addicts are still highly sensitized and hence, highly vulnerable to relapse.

Ad.2. Exposure to drug-related stimuli. Concerning exposure to drug-associated stimuli, very much the same mechanisms seem to operate as with taking the drug itself (priming):

- Through associative learning processes (classical conditioning), not only the drug itself but also drug-associated stimuli have gained increased incentive properties;
- Studies have indicated that conditioned incentive stimuli act much like a priming dose of the drug itself similarly (although to a lesser extent) producing an increase in mesolimbic dopaminergic activity.

Ad.3. Exposure to emotional stress. For emotional stress acting as a trigger for relapse, a simple and straightforward explanation may be that drug use (or relapse into drug use) may provide an escape from stress for the individual. Alternatively:

- In animal experiments, both stress and drug use have been shown to activate and sensitize the dopaminergic system, thereby increasing the incentive-motivational properties of drugs and drug-related stimuli;
- Studies have indicated that animals repeatedly exposed to drugs are hypersensitive to stress, and conversely;
- Animals repeatedly exposed to stress are hyperresponsive to the incentive-motivational properties of drugs.

Are addicts merely the victim of their own brain processes?

Reviewing much of the animal literature on craving (which in animal experiments is operationalized in behavioral terms) and relapse (which in animal studies is operationalized as the reinstatement of drug-seeking and drug administration by animals pretreated with a drug), it seems as if craving and relapse are merely the combined product of (nonconscious) associative learning processes and progressive sensitization of certain neurotransmitter systems, which in turn result in hyperresponsivity to incentive drug-properties. Stated this way, relapse very much ‘sounds’ like the inevitable outcome of an automatic process, on which the individual has little or no influence.

Notwithstanding their strengths, the currently used animal models have some important limitations with regard to their meaning for human behavior. For example, in contrast to the day-to-day circumstances of human addicts, most paradigms in animal studies do not include the presence of multiple incentive drug-stimuli simultaneously (e.g. cocaine, heroin, alcohol), the behavioral alternatives of the animal are often very limited (the animal can press a lever or not), and the influence of contextual factors and presence of non-drug incentive stimuli (e.g. food, sex) on drug self-administration is rarely taken into account.

In real life, we know that people make choices and apply cognitive control strategies, which codetermine whether a lapse or the exposure to drug-associated stimuli or the experience of emotional stress will actually result in a full-blown relapse. To the extent these factors evoke subjectively experienced craving, one could – simplified – state that a relapse will not occur if the level of control is higher than the level of craving. To emphasize the importance of control, this presentation is concluded with a brief selection of some of the typical cognitive factors that codetermine the outcome of the relapse process:

- Self-efficacy. In various studies, the level of self-efficacy – in this context the degree of confidence in staying abstinent in specific situations – has been demonstrated to be predictive of treatment outcome, in terms of whether a relapse will occur. Perhaps even

more significant among those who relapse, specific self-efficacy areas have been shown to be predictive of specific relapse situations.

- Outcome expectancies. Although primarily investigated in the field of alcohol research, but relevant for both alcohol and drug abuse, outcome expectancies about the effect of a substance have been shown to be an important mediator of the relapse process. Outcome expectancies incorporate both a cognitive and a motivational component, referring to an individual's information about the drug effect from previous experiences and the reinforcement properties of the substance for the individual respectively.
- Attributions. If a lapse occurs, the lapse can be attributed by the individual to either internal or external factors. In general, the probability of a subsequent full-blown relapse is reduced if the person attributes the lapse to changeable and controllable factors, either externally (e.g. 'only this situation caused me to drink again, but I won't drink in other situations'), or internally (e.g. 'I did not try hard enough'). If a lapse is attributed to unchangeable and uncontrollable factors (e.g. 'I am not strong enough and never will be'), a subsequent relapse is more likely to occur.
- Decision-making. A last important cognitive factor is the decision-making process itself. From many studies (and sometimes from personal experience) we know that decisions about important personal matters evoke psychological and emotional stress, and that decisions under stress tend to be hasty, irrational, and under the influence of selective attention to the various options involved in the decision.

In the context of clinical practice (e.g. relapse prevention interventions), it may very well be that most progress in the near future can be expected from cognitive-behavioral interventions (including cue exposure therapy and coping-skills training) which focus on the output side of the brain processes discussed.

Behavioral and Neurobiological Factors Involved in Drug Craving and Relapse: A Preclinical Perspective

Louk Vanderschuren

Drug addiction is a chronic relapsing disorder characterized by motivational disturbances such as drug craving (defined as excessive drug wanting) and compulsive drug-seeking behavior. In recent years, a lot of research has been devoted to an animal model of craving, the reinstatement of drug-seeking behavior model. In this model, animals are trained to self-administer a drug, such as heroin, cocaine, nicotine or alcohol. When stable levels of self-administration are reached, the animals experience a period of drug abstinence, during which operant behavior (lever pressing, nose poking) is no longer reinforced by drugs and will therefore become extinguished. Subsequently, drug-seeking behavior (non-reinforced operant behavior) can be reinstated by a variety of stimuli, such as drugs, drug-associated (conditioned) cues, and stressors. Remarkably, craving in drug addicts can be precipitated by these same stimuli (drugs, drug-associated stimuli, and stressful experiences), which supports the validity of the reinstatement model as an animal model of drug craving. Using this animal model, preclinical research has focused on revealing the neuronal circuits involved in drug craving.

According to the incentive sensitization theory of addiction, drug craving is the result of long-lasting adaptations within the neuronal circuitry involved in motivational behavior caused by exposure to drugs. In laboratory animals, these neuroadaptive phenomena become manifest as a persistent hyperresponsiveness to certain behavioral effects of drugs, which is termed behavioral sensitization. In support of this theory, we have recently shown that the ability of opioid and dopaminergic drugs to evoke expression of behavioral sensitization predicts their ability to reinstate drug-seeking behavior upon long-term extinction from intravenous self-administration. This suggests that the neuronal mechanisms underlying expression of behavioral sensitization are also involved in craving evoked by drug exposure. Research into the neurobiology of behavioral sensitization has pointed out that, alongside a wide variety of neuroadaptations, many of which are drug-specific, hyperresponsiveness of the mesolimbic dopaminergic system (projecting from the ventral tegmental area (VTA) to the nucleus accumbens) is a common feature of long-term sensitization induced by different kinds of drugs, such as heroin, morphine, cocaine, amphetamine, nicotine and alcohol. Likewise, the mesolimbic dopaminergic system has also been shown to be critical for drug-induced reinstatement of drug-seeking behavior. Research into the neuronal factors involved in drug-cue and stress-induced reinstatement of drug-seeking behavior has only just started. Thus, drug cue-induced reinstatement has been shown to depend upon the basolateral amygdala. Stress-induced reinstatement involves release of corticotropin-releasing factor within the bed nucleus of the stria terminalis and is under inhibitory influence of the septum. Together, these data suggest that reinstatement of drug-seeking behavior evoked by drugs, cues, or stress, at least in part, relies upon distinct neuronal circuits.

Future research in our laboratory is directed at further unraveling the neuronal circuits involved in drug-seeking behavior evoked by these various stimuli, with emphasis on possible common systems, i.e. the endpoint systems involved in drug-seeking behavior in general. To that aim, both behavioral and anatomical approaches will be employed. With regard to the former strategy, we will attempt to either evoke or inhibit drug-seeking behavior by locally injecting drugs (opioid, dopaminergic and glutamatergic drugs) into discrete brain areas thought to be involved in drug-seeking behavior (nucleus accumbens, medial prefrontal cortex, VTA, amygdala). In addition, using animal models for attention (such as the 5-choice serial reaction time task) and impulsivity (delayed reward task), the effects of repeated drug (self-) administration on these cognitive processes and their role in relapse to drug-seeking behavior will be investigated. In the anatomical approach, neurons

activated during drug-seeking will be visualized by means of expression patterns of IEGs (c-Fos, zif-268) and plasticity related proteins (phospho-CREB, syntaxin) in the brain areas mentioned above.

Discussion

Ingmar Franken

Definition of craving

From a research point of view, it is fruitful to create more consensus about the definition of craving. In the past, several consensus meetings on this topic have been arranged. Nevertheless, there is still no accord between researchers on this definition. The proposal is put forward to use as broad as possible definition without excluding potentially important concepts and mechanisms in advance. Because the craving research and craving knowledge is only in a premature stage, it is too early for narrowing the definition. In addition, it was discussed that it may be that there is not such a thing as one definition of craving, there may exist several subtypes of craving. When a subclassification of craving will be made, it is desirable that valid animal models of this subtype can be found. For example, anticipation of drug use may be a subtype of craving. This anticipation of an expected drug infusion can also validly be modeled by animal studies where this anticipation expresses itself in hyper-activity of the animal.

When craving is viewed merely as a subjective state, the interpreting of results of animal studies on craving is difficult as result of the impossibility of measuring subjective states in animals. However, craving is not a subjective state alone. In addition to animal studies, in which craving can only be observed indirectly by the subsequent behavior of rats, in human study it is possible to investigate the subjective state by asking a person whether he or she experiences craving. Although it is not in question whether other animals do have subjective states, these states can only be measured by the resulting behavioral correlate of this subject state.

It is frequently observed that drug addicts do not report craving before relapse. Although much of these observations are the result of the methodological flaws of retrospective studies, it is possible that in some persons craving does not always precede relapse. In the past, it was proposed that craving can occur outside consciousness. It seems, however, not useful to introduce the term unconscious with respect to subjective states. It raises other difficulties when the statement is held that a feeling or emotion can be unconscious. It may be more useful to speak of triggered automatic responses without the conscious feeling of craving. As stated before, there may be different kinds of craving. For instance, craving can be the result of wanting the positive reinforcement of the drug or avoiding the current negative state by using the drug. It may be that the in the latter situation craving is less conscious experienced than in the first situation.

Craving can be regarded as the subjective motivational state that accompanies approach tendencies. Currently, research is going on in which two possible pathways of drug approach mechanisms are being studied. One pathway to drug approach action is by means of cue-elicited craving. Another pathway may be that the drug approach mechanism is triggered by cues without the awareness of craving, an automatic response.

Craving in non-chemical addictions

One of the topics that arose was the role of sensitization in non-chemical (behavioral) addictions such as gambling. All animal studies focus on sensitization as the result of psychoactive substances. However, in gamblers, a comparable behavioral sensitization can be observed without the administration of psychoactive substances. Two major problems occur when studying sensitization in gambling. First, currently there is not a valid animal paradigm to simulate gambling in rats. Possibly, alternative rewards may simulate the monetary reward. Second, it is difficult to show sensitization in humans. Currently, only two studies (Strakowski et al. 1996, 1998) have shown some evidence for sensitization in humans A problem is that sensitization studies in human subjects raise ethical problems. Drug naive subjects should be repeatedly exposed to drugs of abuse. It would be interesting to compare the effects of exposure to other potentially reinforcing stimuli, such as erotic cues, and drug stimuli. A study by Childress et al. has shown that there are similar neural pathways involved in both erotic and drug craving. In both exposure situations an increase in dopaminergic activity has been observed.

Therapy

Craving can be regarded as a subjective state or as an emotional state. In the latter case, it is more like a mood state. In this case, cognitive factors such as expectancies are predictors of drug intake, yet not a correlate of craving. From the clinical point of view, cognitive factors may be of major importance. A therapist can alter the expectancies of drug outcome or enhance self-efficacy to refuse drugs. Studying memory may lead to new insights in the concept of craving. The incentive properties of cues, the role of the environment in triggering relapse, are all based on memories. The cortex plays an important role in modifying the output. Cognitive therapy can bring in more control by activating the cortex and gating the sensitivity of subcortical systems. This cortical gating may differ from person to person, however we do not know which personal differences play a role in this function. Dr. Robinson and Crombag have done some work on the effects of new environments on the sensitivity of the dopaminergic system. These studies show that a novel environment can serve as a stressor and hypersensitize the dopaminergic system involved in drug use and relapse.

Clinical relevance

The question is asked whether cross-sensitization between opiates and psychostimulants observed in rats has some clinical relevance. Thus, Vanderschuren, De Vries and Schoffelmeer have shown that animals pre-exposed to opiates are hypersensitive to psychostimulants, but

not vice versa. These findings, and other reports in the literature showing that exposure to certain drugs of abuse can cause altered behavioral reactivity to other types of drugs, might have some relevance for research into polydrug abuse. In general, it was concluded that it is a fruitful enterprise to take more mutual cognizance of animal and human studies in the field of craving and relapse.

Workshop IV: Principles of Effective Addiction Treatment

Pharmacotherapies and Behavioral Models

Cor de Jong

Opioid dependence is a chronic, relapsing disorder. At the present the accepted detoxification method is replacement of herion by methadone, followed by gradual lowering of the dose. This method is safe but it is also associated with high drop-out and relapse rates. Administration of an opioid antagonist results in rapid detoxification. The detoxification under general anesthesia is the most rapid way to realize detoxification. No randomized trials are available to evaluate the value of rapid detoxification under general anesthesia.

The aim of EDOCRA is to assess the Effectiveness of Detoxification with or without general anesthesia, combined with the administration of an Opioid antagonist and biopsychosocial rehabilitation based on the Community Reinforcement Approach (CRA). The study is a randomized, open label multi-center trial. Patients will be randomized over two detoxification groups with or without general anesthesia, combined with the administration of an opioid antagonist and biopsychosocial rehabilitation based on the CRA.

Research questions are:

1 Is rapid detoxification using naltrexone under general anesthesia combined with the administration of an opioid antagonist and biopsychosocial rehabilitation more effective in terms of opioid abstinence than rapid detoxification using naltrexone without general anesthesia?

2 Is there a difference in medical costs between the rapid detoxification with or without general anesthesia combined with the administration of an opioid antagonist and biopsychosocial rehabilitation?

3 Do patients' characteristics such as demographical, severity of addiction, psychopathology, withdrawal symptoms or craving, have predictive value on the effectiveness of rapid detoxification with or without general anesthesia combined with the administration of an opioid antagonist and biopsychosocial rehabilitation?

The total number of patients for randomization is 320 (160 per treatment strategy) at four centers: Jellinek in Amsterdam, Kentron in Breda, Novadic in St. Oedenrode and Parnassia in The Hague. The Free University of Amsterdam, the University of Amsterdam, The University of Nijmegen and the University of Leiden are involved in the study.

Does Psychosocial Treatment Enhance the Efficacy of Acamprosate in Patients with Alcohol Problems? Results of a Randomized Clinical Trial.

Gerard M. Schippers

In this presentation the results were presented of a Randomized Clinical Trial (RCT) done in the Netherlands with acamprosate and brief behavioral interventions. The goal of this study was to examine whether adding a psychosocial intervention to the medical prescription of acamprosate enhances treatment outcomes.

Method: 241 patients who met the DSM-IV criteria for alcohol dependence or abuse were randomized into one of three treatment conditions: acamprosate; acamprosate plus minimal intervention based on motivational enhancement (3 weekly sessions of 20 minutes); and acamprosa-te plus brief cognitive-behavioral therapy (7 weekly sessions of one hour). Both psychosocial interventions were manual-guided and treatment integrity was controlled for. Pharmacotherapy was provided for 28 weeks. Patients were assessed prior to treatment (baseline) at the selection and the inclusion visit. During the treatment drinking behavior and medication compliance were assessed in week 2, 4, 10, 16, 22, and 28.
Psychological distress was assessed in week 10 and 28. Follow-up of drinking behavior and psychological distress took place 6-months after termination of pharmacological treatment.

Results: Of 241 patients 114 (47.3%) remained in treatment for 28 weeks. The mean percentage of abstinent days for the total group of patients was 56.7% in 28 weeks of treatment (ITT sample). During the last 6 weeks of the 28-week treatment period, 18.2% of the patients in group 1, 24.4% of group 2 and 17.9% of group 3 (ITT) and 36.8%, 47.7% and 42.4% respectively of the per protocol sample were abstinent. The mean number of drinks per day for relapsers during treatment were 6.6, 5.9 and 6.3 respectively, compared to mean baseline drinking of 15.3 drinks per day.
Of the ITT population, 169 patients (70.1%) were seen for follow-up. Respectively 7.8%, 14.0% and 9.0% of the patients were continuously abstinent between the end of treatment and follow-up assessment (ITT).

None of the statistical analyses revealed significant differences between treatment groups for any of the drinking outcomes both at the end of 28 weeks of treatment and at six month follow-up. There were also no statistically significant differences in medication compliance, drop-out rates and psychological distress between treatment conditions.

Conclusions: The results indicate that brief psychosocial interventions do not add to the efficacy of acamprosate. On the one hand it might be that more intensive psychosocial interventions are needed to really improve treatment results. On the other hand, one could conclude that the medical prescription of acamprosate without additional psychosocial intervention is a realistic and sufficient treatment option, at least for a certain group of patients. Another explanation might be that sample selection was biased. It is possible that patients who were motivated for psychosocial treatment refused participation in the trial, because of the high chance of not being referred to a therapist. The general idea, however, that pharmacotherapy in alcohol dependence should always be combined with some form of psychosocial intervention could be debatable.

Discussion

Ien van de Goor

In the discussion the moderators Dr. Rawson and Sineke Ten Horn asked the participants to formulate themes for cooperative research. Three themes were already identified earlier:

- cooperative efforts to develop instruments to measure treatment outcomes and the contents of treatment programs;
- comparative longitudinal studies with existing data sets on natural treatment histories;
- experimental clinical trials with different treatment models (for polydrug users and for benzodiazepine users) in both countries.

More suggestions were added in the discussion concerning systematic reviews of training for therapists and social workers; adding Dutch cities as an extra site to large scale clinical trials in the United States; comparing information on ethnic minorities e.g. on alternative treatment and finally analyzing theoretical models of addiction and addiction treatment. The discussion closed with some information on possibilities for grants from NIDA and the Dutch Addiction Program.

Workshop V: Monitoring Illicit Drug Use and Reaching Out to Difficult- to-Reach Populations

Summery of the presentations of Dirk J. Korf, Peter Blanken, Dike van de Mheen en Inge Spruit

Inge Spruit

Presentation of Dirk J. Korf

Dr. Korf, one of the moderators of the workshop, started by summarizing the most important findings of the discussions during the U.S. – Netherlands Addiction Workshop held on the previous day. Good prospects for future cooperation between the United States and the Netherlands were discussed. These research projects should always contain a qualitative element, be relevant for both countries, and have an added value. Potential themes for international comparative research include gender differences such as female use patterns or the role of females in networks; new users of synthetic drugs; and culture, rituals, and policy.

Presentation of Peter Blanken

Peter Blanken outlined the potential contribution of a community-based Drug Monitoring System (DMS) in monitoring and understanding changes in drug use patterns and their consequences among marginalized, almost daily users of opiates and (crack-) cocaine. The DMS combines quantitative and qualitative data that are collected through ethnographic community fieldwork, small-scale sample surveys among specified target groups, and a network of key contact persons. The goal of the DMS is to supply up-to-date information for the benefit of policy makers, drug users, drug treatment agencies and research scientists. The DMS addresses size and sociodemographic characteristics of the target group; drug use patterns (type of drugs, route of administration, mechanisms of self-regulation); nature and severity of problems in the area of physical health, employment, legal status, social and psychiatric functioning (Addiction Severity Index-problem areas); and mobility of the target group(s). Furthermore, the DMS is organized in such a way that any other relevant information related to drugs, drug use, or users (such as new types of drugs, new trends) are detected and can be monitored as well. He presented some results - based on five years combined quantitative and qualitative DMS field research - on the interrelationship between (crack-) cocaine smoking patterns, retail level drug dealing and local drug policy, and he discussed the role of active drug users ('community field workers') in a community-based drug monitoring system.

In the second part of the presentation he briefly outlined the Dutch trial on the effectiveness of medically co-prescribed heroin, focusing on the protocol that is currently being developed to evaluate the acceptance of medically co-prescribed heroin treatment and monitor and evaluate the psycho-social changes that occur among participants in the trial.

Presentation of Dike van de Mheen

Dike van de Mheen concentrated on how monitoring, especially the results of the DMS studies, may influence local drug policy, prevention and treatment and how, the other way around, local drug policy, prevention and treatment influence the drug monitoring system. For example, one of the Rotterdam studies found illegal selling of methadone, which may prompt the methadone program to change its dispensing policy. The other way around: local policy prompted the Heerlen monitoring system to focus on drug tourism and heroin prostitution. She said monitoring balances between providing 'quick-and-dirty' information and scientifically sound research. Effective monitoring programs should obtain both quantitative and qualitative data, provide information about out-of-treatment drug abusers, and seek cooperation with other sectors.

Presentation of Inge Spruit

Inge Spruit called the most important characteristic of monitoring its power to combine an epidemiological and social sciences approach, bringing to the forefront that its questions and research results are relevant to policy, prevention and assistance. When monitoring takes place in the field of illicit drugs and drug use:

– A qualified monitor will always demand a targeted combination of quantitative research, including the repeated measurement of standardized core indicators, as well as qualitative research on questions dictated by the empirical social reality at the current time and place and the limitations of quantitative research methods.

– Research into hidden and/or difficult to reach groups is indispensable for a responsible monitor in this field (even if such groups would not importantly influence prevalence or incidence figures) because these may be: groups with a high level of social, health, addiction or other problems; high (multiple) risk groups; groups of special importance for interventions, demand reduction, prevention, assistance; groups of special interest for questions related to understanding drug questions (e.g. characteristics of social groups influencing drug careers, e.g. trend setters); new drug users or users setting trends for new patterns of use; users who pose specific demands on the community, (local) drug policy; etc.

She invited participants to identify themes for internationally cooperative research, suggesting that workshop participants focus the discussion on the exploration of similarities and differences between (and within) the United States and the Netherlands that could support, reject or influence research.

APPENDICES

Appendix A

Workshop and Symposium Program and Participants

U.S. – Netherlands Addiction Workshop
Setting the agenda for drug abuse and addiction research cooperation between NIDA and ZON/NWO
Tuesday October 19, 1999

Binational Symposium on Drug Abuse and Addiction Research and Innovation
Wednesday October 20, 1999

Trippenhuis, Royal Netherlands Academy of Arts and Sciences / KNAW, Amsterdam
Organized by:
- Netherlands Research and Development Program on Substance Use and Addiction (Programma Verslaving)
- National Institute on Drug Abuse, National Institutes of Health, United States of America (NIDA)

In cooperation with:
- Amsterdam Institute on Addiction Research (AIAR)
- Netherlands Institute of Mental Health and Addiction (Trimbos-institute)

Program U.S. – Netherlands Addiction Workshop, October 19, 1999

Program U.S.–Netherlands Addiction Workshop, October 19, 1999

10.00 Welcome and Coffee

10.30 Opening by the Chairmen of the Day Jan M. van Ree & Alan I. Leshner
Signing of the Exchange of Letters by Eduard Klasen, Alan I. Leshner & Henk J. Smid

10.45 M. Patricia Needle & Eduard Klasen:
Aims of cooperation and ways to stimulate cooperation

11.00 Presentation of possible themes for cooperation
1 Kathleen Merikangas: Risk, resiliency and vulnerability
2 Henk Rigter: Addiction prevention
3 Terry Robinson: Multidisciplinary research on relapse and craving
4 Wim van den Brink: Drug abuse treatment
5 Claire Sterk: Monitoring of drug use and reaching difficult-to-reach groups

13:00 Lunch

13.30 Parallel gatherings of researchers
In five parallel sessions the participants will present and discuss ongoing top research in their respective countries with a specific focus on promising lines of collaboration between researchers from the two countries. Together they should formulate (maximally) three themes for cooperation to be presented at the following plenary session.

1 Research on risk, resiliency and vulnerability
Wim van den Brink (moderator), Mirjam Gerrits, Kathleen Merikangas, Ton Schoffelmeer, Reinout Wiers
2 Addiction prevention
C. Hendricks Brown (moderator), Alfons Crijnen, Pim Cuijpers, Henk Rigter
3 Multidisciplinary research on relapse and craving
Stephen T. Higgins (moderator), Anita Jansen, Gerard M. Schippers, Roel Verheul, Taco de Vries
4 Research on drug abuse treatment (pharmacotherapies and behavioral models)
Richard Rawson (moderator), Vincent M. Hendriks, Cor de Jong, Louk Vanderschuren, Frans Zitman
5 Research on monitoring drug use and reaching difficult-to-reach groups
Dirk J. Korf (moderator), Peter Blanken, Dike van de Mheen, Inge Spruit, Claire Sterk

16.00 Plenary summary and conclusion chaired by Alan I. Leshner & Jan M. van Ree
The proposals from the five sessions are presented plenary. Themes can be reformulated, combined or removed. The meeting should end with determining maximally ten themes (possibly less as a result of combination and elimination of overlap) with serious potential for significant, innovative, quality research collaboration, which has additive value for addiction research in both countries. The themes are presented to the funding organizations NIDA and ZON/NOW. Investigators in the two countries will prepare joint grant applications for review within NIDA and NIH.

17.00 Closing and proposed dates for next year's meeting in the United States

17.30 Boat tour

19.00 Dinner
Restaurant De Silveren Spiegel (the Silver Mirror), Kattegat 4-6, Amsterdam
Program Binational Symposium on Drug Abuse and Addiction Research and Innovation October 20, 1999

Program Binational Symposium on Drug Abuse and Addiction Research and Innovation, October 20, 1999

Chairs of the day: M. Patricia Needle and Sineke ten Horn

09.00 Registration and coffee

09.45 Opening by Dutch Minister of Health, Welfare and Sport
Els Borst

10.00 Drug Abuse Research in the New Millenium: Challenges and Opportunities
Alan I. Leshner

10.30 Risk, resiliency and vulnerability: Individual differences in susceptibility to addictive substances (biomedical and behavioral research)
NL: Mirjam Gerrits
US: M. Patricia Needle

11.00 Coffee break

11.30 Principles of effective prevention
NL: Henk Rigter
US: C. Hendricks Brown

11.30 Relapse and the role of craving
NL: Ton Schoffelmeer
US: Terry Robinson

12.30 Lunch

13.30 The role of pharmacotherapies in addiction treatment (biomedical research)
NL: Wim van den Brink
US: Richard Rawson

14.00 The role of behavioral models in addiction treatment (behavioral research)
NL: Gerard M. Schippers
US: Stephen T. Higgins

14.30 Monitoring illicit drug use and reaching difficult-to-reach groups
NL: Dirk J. Korf
US: Claire Sterk

15.00 Tea break

15.30 Workshops

17.00 Informal gathering

Workshops:

I Risk, resiliency and vulnerability
Moderators: Marjan Joëls (NL) and M. Patricia Needle (US)
Presentations: Taco de Vries and Reinout Wiers

II Principles of effective prevention
Moderators: Henk Rigter (NL) and C. Hendricks Brown (US)
Presentations: Alfons Crijnen and Pim Cuijpers
Report: Wilma Vollebergh

III Relapse and the role of craving
Moderator: Frans Zitman (NL) and Terry Robinson (US)
Presentations: Vincent M. Hendriks and Louk Vanderschuren
Report: Ingmar Franken

IV Principles of effective addiction treatment: pharmacotherapies and behavioral models
Moderators: Sineke ten Horn (NL) and Richard Rawson (US)
Presentations: Cor de Jong and Gerard M. Schippers
Report: Ien van de Goor

V Monitoring illicit drug use and reaching out to difficult to reach populations
Moderators: Dirk J. Korf (NL) and Claire Sterk (US)
Presentations: Inge Spruit, Peter Blanken, Dike van de Mheen

Participants

Workshop participants and symposium presentators

From the United States of America

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Since 1994 dr. Alan I. Leshner has been director of the National Institute on Drug Abuse (NIDA), one of the scientific institutes of the U.S. National Institutes of Health. NIDA supports over 85% of the world's research on the health aspects of drug abuse and addiction. Dr. Leshner received his undergraduate degree in psychology from Franklin and Marshall College, and the M.S. and Ph.D. degrees in physiological psychology from Rutgers University. He has been elected a fellow of many professional societies, and has received numerous awards from both professional and lay groups for his national leadership in science, mental illness and mental health, and substance abuse and addiction. In 1996, President Clinton conferred the Presidential Distinguished Executive Rank Award on Dr. Leshner, the highest award in Federal service. In the fall of 1998, Dr. Leshner was elected to membership in the

Institute of Medicine of the National Academy of Sciences. Prior to coming to NIDA, Dr. Leshner was the Deputy Director and Acting Director of the National Institute of Mental Health. He went to NIMH from the National Science Foundation (NSF), where he held a variety of senior positions, focusing on basic research in the biological, behavioral and social sciences, and on science education. Dr. Leshner went to NSF after 10 years at Bucknell University, where he was Professor of Psychology. While on the faculty at Bucknell, he also held long-term appointments at the Postgraduate Medical School in Budapest, Hungary, at the Wisconsin Regional Primate Research Center, and as a Fulbright Scholar at the Weizmann Institute of Science in Israel. Dr. Leshner's research has focused on the biological bases of behavior. He is the author of a major textbook on the relationship between hormones and behavior, and numerous book chapters and papers in professional journals. He also has published extensively in the areas of science and technology policy and education.

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He is principal investigator of EDOCRA, a randomized multi-center study in patients with opioid dependence on the Effectiveness of Detoxification combined with the administration of an Opioid antagonist and an approach of bipsychosocial rehabilitation, based on the Community Reinforcement Approach, focused on abstinence of opioids.

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Dr. Inge Spruit started her career at the Leyden University in the field of public health and community medicine. At present she is head of the Department of Monitoring and Epidemiology of the Netherlands Institute of Mental Health and Addiction (Trimbos-institute). The core business of the department's program on addiction epidemiology is monitoring the use, and patterns of the use and misuse, of illicit drugs and alcohol, and the consequences of such use (socially, mortality, morbidity, use of care and assistance facilities) among the Dutch population in general and among special groups (for example high-school students, drop-outs). The monitors include quantitative as well as qualitative research among people, but also chemico-toxicological monitoring of the composition of illicit drugs. Important questions of the epidemiological research of the department focus on the determinants of the use of drugs and misuse of alcohol, drug- and alcohol using careers and the effects of interventions.

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Appendix B

Funding Mechanisms To Support Collaborative Research

Building international research collaborations requires participation in networks of scientists within countries, within regions, and worldwide who can successfully engage in collaborative research on drug abuse and drug-related health consequences. NIDA promotes international scientific collaboration in drug abuse research through technical workshops, binational and multinational professional meetings and research symposia, scientific and technical consultations, and other professional development programs.

Fellowship Programs

The NIDA International Program supports professional development through two international research fellowships. Participation in a NIDA-supported fellowship program provides researchers from outside the United States with invaluable training in U.S. research methodologies and the NIH grants application process. U.S. drug abuse researchers who serve as mentors to NIDA-supported Fellows have a unique opportunity to work with researchers from outside the United States.

– *INVEST Research Fellowships* are competitive, one-year fellowships for scientists from outside the United States to conduct postdoctoral research with a NIDA-funded researcher. Fellows receive an orientation program at NIDA and travel support to attend scientific meetings. Fellows and their mentors jointly develop a collaborative research proposal for implementation in the Fellows' home countries.

– *NIDA Hubert H. Humphrey Drug Abuse Research Fellowships* are competitive, 10-month fellowships for midcareer professionals from eligible countries that combine academic course work at The Johns Hopkins University with professional development activities, including travel support to attend scientific meetings and a professional research affiliation with a NIDA grantee.

– *NIDA Distinguished International Scientist Collaboration Awards* are competitive 1-3 month professional visits to the United States for experienced drug abuse researchers from any other country to stimulate development of innovative collaborative research. This program will give senior international researchers the opportunity to propose projects that can potentially advance the scientific agenda in both countries as well as offer the ability to apply enhanced research skills and mechanism in the non-U.S. scientist's home country.

Research Grants

Finding the most appropriate funding mechanism for international research collaborations can be a crucial part of a research project. NIDA funds approximately 85% of the world's research on drug abuse and its consequences. Most of the drug abuse research sponsored by NIDA is conducted by scientists in universities and other organizations and is funded through the NIDA extramural research program. Through a competitive, peer-review process, research grants are awarded by NIDA on a regular basis. There are several opportunities for NIDA/National Institute of Health (NIH) support for international collaborative research through grants mechanisms:

- *Administrative supplements* to existing grants can be proposed by NIDA grantees for a maximum of $100,000 per year or 25% of the direct costs of the grant (whichever is less). The added component must be related to the purpose and integrity of the original grant. The proposal is not scored competitively through NIH, but approval and budgetary sign-off within NIDA are required.

- *Domestic grants* with a foreign component enable U.S.-based principal investigators to conduct cooperative international studies. The foreign component is part of the original grant; the entire application is scored competitively.

- *Foreign grants* allow researchers from outside the United States to compete for funding within the NIH system. The actual research is conducted outside the United States. For a grant to be awarded to a foreign institution, the principal investigator must demonstrate a special opportunity to further drug abuse research through the use of expertise, resources, populations, or environmental conditions not readily available in the United States.

Other Funding Opportunities

Other NIH programs are administered through the Fogarty International Center and support professional development opportunities or international research collaborations:

- *Fogarty International Research Collaboration Awards (FIRCA)* provide up to $32,000 per year, for up to 3 years, for international research partnerships between NIH-supported scientists and collaborators eligible countries. The FIRCA goal is to extend and enhance the research of the U.S. investigators while benefitting the scientific interests of international scholars.

- *AIDS-FIRCA* grants support cooperative studies by NIH grant recipients and foreign institutions on HIV/AIDS and on new and re-emerging infectious diseases. AIDS-FIRCA grants are available for collaborative research in all countries. Support is similar to that available through the FIRCA grants.

- *Specific country grants.* Research funds occasionally become available through sources targeted to a specific country or region. One example is the Japan Society for the Promotion of Science.

- *AIDS International Training and Research Program (AITRP)* is sponsored by the Fogarty International Center to enable scientists from eligible countries to increase their proficiency to undertake biomedical and behavioral research related to AIDS and to develop and use those acquired skills in clinical trials and prevention and related research. AITRP has a new focus on training international health professionals in research on HIV infection among drug-using populations.

- *International Training and Research Program in Emerging Infectious Diseases (ERID)* enables U.S. universities and nonprofit research institutions to support international training and research programs for foreign scientists and public health workers from eligible nations in research, control, and prevention strategies related to emerging and reemerging infectious diseases. The ERID award is an institutional training grant.

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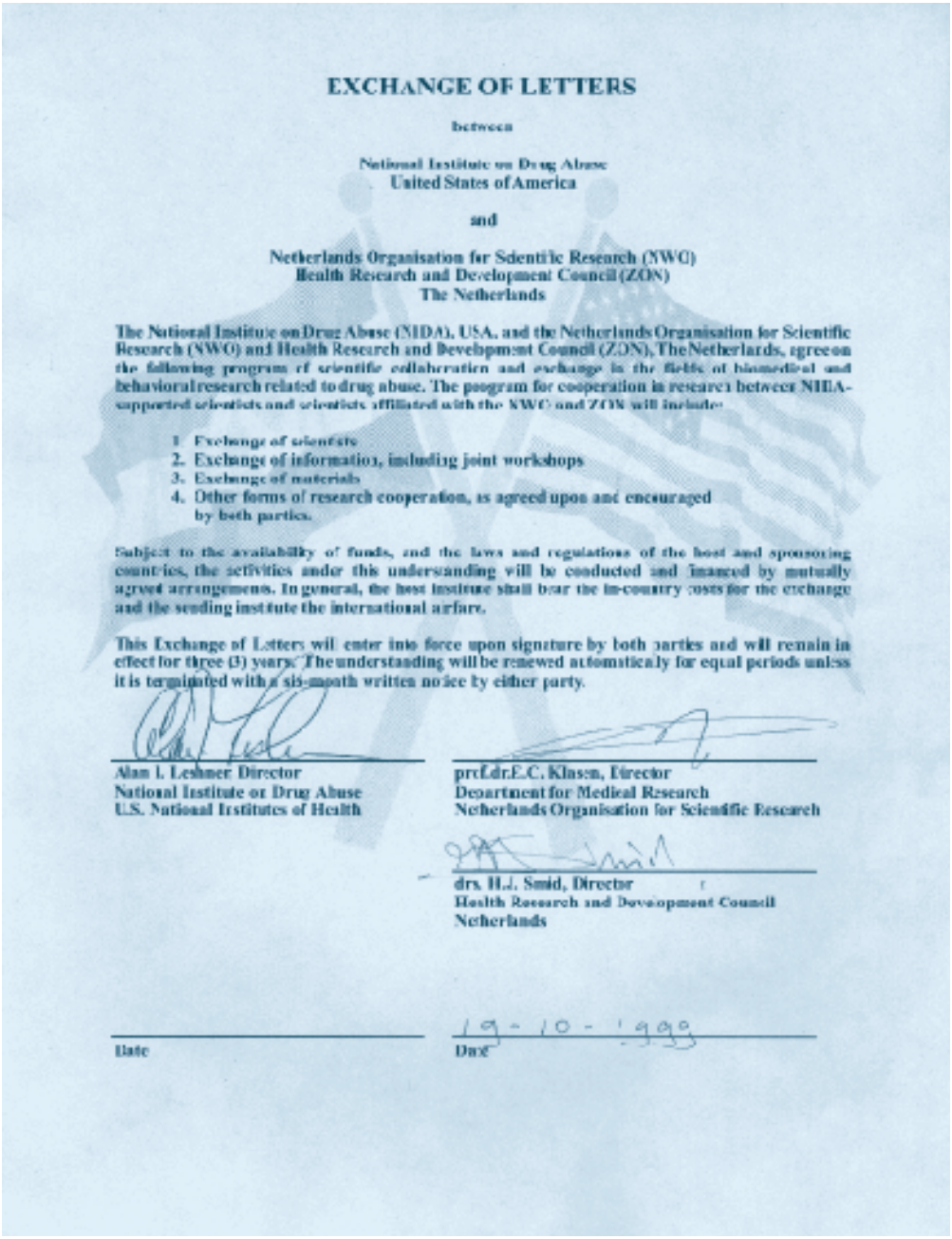
Appendix C

Exchange of letters



EXCHANGE OF LETTERS

between

National Institute on Drug Abuse
United States of America

and

Netherlands Organisation for Scientific Research (NWO)
Health Research and Development Council (ZON)
The Netherlands

The National Institute on Drug Abuse (NIDA), USA, and the Netherlands Organisation for Scientific Research (NWO) and Health Research and Development Council (ZON), The Netherlands, agree on the following program of scientific collaboration and exchange in the fields of biomedical and behavioral research related to drug abuse. The program for cooperation in research between NIDA-supported scientists and scientists affiliated with the NWO and ZON will include:

1. Exchange of scientists
2. Exchange of information, including joint workshops
3. Exchange of materials
4. Other forms of research cooperation, as agreed upon and encouraged by both parties.

Subject to the availability of funds, and the laws and regulations of the host and sponsoring countries, the activities under this understanding will be conducted and financed by mutually agreed arrangements. In general, the host institute shall bear the in-country costs for the exchange and the sending institute the international airfare.

This Exchange of Letters will enter into force upon signature by both parties and will remain in effect for three (3) years. The understanding will be renewed automatically for equal periods unless it is terminated with a six-month written notice by either party.

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Netherlands

Date

19 - 10 - 1990
Date