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PRENATAL ABUSE OF LICIT AND ILLICIT DRUGS

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Preface

To the best of my knowledge, this is the first meeting on prenatal drug use that brings together basic and clinical researchers, epidemiologists, healthcare providers, those concerned with legal and ethical issues, and policy makers. But what makes this conference especially unique is the unusually broad range of drugs that will be discussed. These include major licit substances—alcohol, nicotine and caffeine, as well as the major illicit drugs—opioids, cannabinoids, central nervous system (CNS) stimulants and phencylidine. Traditionally, the public health aspects of these compounds have been assigned to and administratively sequestered in various governmental agencies. The National Institute on Alcohol Abuse and Alcoholism has been concerned exclusively with alcohol. Illicit drugs fall under the purview of the National Institute on Drug Abuse, although this agency also funds basic research on nicotine in both adult and immature organism. At the same time, the National Institute on Child Health and Human Development has a long history of interest in the effects of smoking on human pregnancy.

One result of this compartmentalization is that it has, in part, given rise to increasingly specialized and narrowly focused scientific disciplines, meetings, societies and journals. And while this is all quite understandable as the natural evolution of scientific activity, information has become widely scattered yet, at the same time, isolated in scientific minicommunities. This clearly serves the interests of the specialized practitioners and scientists, enabling them to interact and share mutual technical and scientific problems unique to their endeavors. But inevitably, boundaries have become more rigid and these specialty groups more insular and self-directed with the result that communication between groups has been impeded.

For example, clinicians concerned with drug-exposed infants often view the basic researcher as reducing whole organisms to neurochemical systems, receptors and binding sites, and their mechanistic findings may be dismissed as either tortuously arcane or of ambiguous relevance to their clinical problems. And, indeed, the daily world of the perinatal treatment staff and the one that they publish papers about, consists of women in a compulsive pattern of drug abuse who also happen to be pregnant and are likely to give birth to very sick, at-risk babies that will require highly specialized medical management. Their major concern is to utilize their medical skills to provide increasingly improved healthcare and treatment to these infants to ensure as optimum an outcome as possible.

On the other hand, clinical researchers may not be as well informed about pharmacokinetics or the fundamental pharmacological processes of tolerance, physical dependence and abstinence. To cite an example from the mid-1970s, at that time pediatric lore suggested that the prolonged or subacute abstinence lasting some 4-6 months in infants that had been prenatally exposed to methadone, was the likely result of the persistence and slow clearance of methadone from the babies' CNS. But opioid pharmacologists knew that human adults in withdrawal from either morphine or methadone similarly show a prolonged abstinence. Although the adult symptoms have a different temporal pattern compared with infants, their symptoms do persist for six months or longer and are not associated with the persistence of the drug in the CNS. Thus, what was thought by some pediatricians to be pharmacologically unique to the neonate would have been viewed by an opioid pharmacologist as possibly a minor variation on the adult phenomenon of prolonged abstinence.

Likewise, basic researchers, in their quest to develop animal models, assess risk, and discover mechanisms underlying toxic outcomes while grappling with the intract-

able problem of extrapolation to humans, may suffer from a certain amount of clinical illiteracy. The clinical perinatal abuse literature may be viewed somewhat opportunistically and exploited as a bountiful reservoir that holds the rationale and scientific justification for a basic research grant proposal. Clinical papers may be eagerly scoured for epidemiological excesses and horrific clinical outcomes, all the better to add spice to significance sections of grant applications. But some of these researchers may have no more than a lay understanding of the etiology and psychobiology of drug abuse, and only a superficial appreciation of issues of medical management of the pregnant drug user and care and assessment of drug-exposed neonates. Thus, some attempts to develop animal models may miss fundamental elements of the clinical problem so that the significance of the research findings may be obscure.

So as not to sound unreasonably harsh, I do acknowledge that given such a vast literature and the enormous complexity of the phenomena that we study, it is often difficult to judge appropriately the proper emphasis that should be given specific information. Clearly, we cannot know and be expert at everything, and primary care physicians and clinical and basic researchers each have a different set of goals and priorities. But we must not lose sight of the fact that together, we make up a larger scientific community that shares a common goal: first, to understand the disease mechanisms associated with prenatal exposure to particular classes of drugs; second, to describe the short- and long-term clinical, biochemical and neurobehavioral manifestations that result from such exposure; and third, through the means by which we understand the mechanisms of such drug exposure, to develop specific treatments, management and prevention.

We come together at a time of gloomy foreboding, when some are saying that the country is in the midst of a national tragedy; our neonatal mortality rate is one of the worst of all of the industrial nations, and the poor and disadvantaged have severe economic barriers, not just to advanced medical technology but, shamefully, to the minimum of prenatal care. Drug use in no small way contributes to this overall grim problem. Let us hope that in this conference, as we learn new information and enlarge our conceptual vocabulary, that we may strike a fresh alliance of understanding and ideas so that for each of us and our respective disciplines, our ignorance of these urgent problems may be palpably diminished.

We are grateful to the New York Academy of Sciences for sponsoring this conference. I want to extend special thanks to Drs. Roger Brown and Marvin Snyder and their able staff at the National Institute on Drug Abuse for their efforts in ensuring the funding for it. I must also express my profound appreciation both to the Conference Committee of the New York Academy of Sciences for their help and encouragement in organizing the program, and to Ellen Marks, the Conference Director, and her outstanding staff, for their skillful and efficient labors in stewarding this meeting into reality. Without the finely tuned organizational process that so swiftly and surely goes into motion once a conference is approved, none of us would have found ourselves at this meeting so expeditiously.

Donald E. Hutchings

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PRENATAL ABUSE OF LICIT AND ILLICIT DRUGS [a]

Editor and Conference Chair
DONALD E. HUTCHINGS

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[a] The papers in this volume were presented at a conference entitled Prenatal Abuse of Licit and Illicit Drugs, which was held by the Behavioral Teratology Society, the National Institute on Drug Abuse (National Institutes of Health), and the New York Academy of Sciences in Bethesda, Maryland on September 7-9, 1988.

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Perspectives on the Concern for and Management of Prenatal Chemical Exposure and Postnatal Effects[a]

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Although teratology and developmental toxicology had their experimental beginnings in the early part of this century, the potential for human developmental toxicity due to chemical exposure was not generally recognized until the thalidomide tragedy of the early 1960s.[1] Furthermore, the fact that exposure to chemicals during development might have subtle and long-lasting postnatal consequences in humans was not generally recognized until the late 1960s and early 1970s.[2] Thus, the last 20 years have seen a remarkable increase in the number of reports of chemical effects on development, particularly on the function of the neonate and young child, reflecting in part the heightened awareness by researchers of the potential for such effects.

A number of agents have been reported to have adverse consequences on the neonate and on later development in both humans and animals. At present, at least nine of these agents have sufficient evidence to confirm that they can cause developmental neurotoxic effects in humans.[3] Of these, several are substances of abuse (heroin, methadone, alcohol, cocaine). At least one therapeutic agent (diphenylhydantoin) and one physical agent (x-irradiation) are also documented human developmental neurotoxicants. In addition, there are three environmental chemicals (lead, methylmercury and polychlorinated biphenyls) for which evidence is sufficient to indicate the unique susceptibility of the developing organism to the developmental neurotoxic effects of these agents. Thus, a variety of agents are capable of affecting the unborn child and neonate in devastating and often irreversible ways.

When one evaluates the available data on the developmental toxicity of chemicals, the types of evidence required to indicate that an agent is a developmental toxicant are similar, whether the agent is a therapeutic agent, an abused substance or a physical or environmental agent.[4] The data available are usually most extensive for therapeutic agents or environmental chemicals for which standard testing is required prior to marketing or release into the environment. In fact, testing of certain chemicals specifically for developmental neurotoxicity has recently been added to the overall developmental toxicity testing battery.[5] For substances of abuse, on the other hand, there is no standard testing (unless the drug is a therapeutic agent), and data may be sketchy

[a] Disclaimer. The views in this paper are those of the author and do not necessarily reflect the views or policies of the U.S. Environmental Protection Agency.

or nonexistent until a problem is recognized in humans. Even then, data are gathered primarily by basic science researchers through grant-funded research, and are not necessarily focused to provide a comprehensive evaluation of the developmental toxicity of an agent.

The management and control of exposure to different chemical agents also varies tremendously. For example, therapeutic agents can be carefully controlled via the federal government and the medical community, and are marketed to be prescribed for certain uses, although misuse does occur. Environmental agents are also regulated by the federal government, and their release into the environment can be controlled to some extent. However, with them there is a much greater potential for misuse and exposure of unsuspecting individuals.

Unfortunately, the management and control of exposure to substances of abuse is much more difficult or impossible. Thus, the contribution by substances of abuse to the overall incidence of developmental toxicity is significant, and may be increasing. In the growing and changing environment of drug abuse in which we live, it is important to educate the general public about the drastic consequences of such abuse during pregnancy. This conference comes as an appropriate step in heightening that awareness among researchers, clinicians, and government officials. I only hope that it will stimulate health care and public health organizations, as well the media, to communicate these concerns and problems to the public, and to provide appropriate education concerning the use of drugs and chemicals during pregnancy.

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Evolution of American Attitudes Toward Substance Abuse

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Anyone who has followed the drug problem for the last ten or fifteen years will have noted an interesting transformation. Cocaine has moved from being perceived as a relatively harmless tonic worthy, according to some drug experts in the 1970s, of decriminalization on those grounds, to being seen as a most dangerous substance with no redeeming qualities. Its earlier merits, euphoria and central nervous system stimulation, are now seen as seductive dangers.[1] This change in attitude toward cocaine may be a paradigm of our pattern of response to a number of powerful chemicals—opium, morphine, cannabis and alcohol. What is even more interesting, this evolution of American attitudes toward substance use and abuse has not happened only once. One might expect that a lesson is learned once and for all, but curiously, in some instances, changes in attitude recur. We may not recall the earlier change in attitude toward cocaine around 1900, but we have been experiencing a close parallel to that cocaine epidemic, at least to 1988. Perhaps the public's almost total lack of knowledge of that earlier time is one powerful reason why we have repeated this "experiment in nature."

Let us think back to that first epidemic. For millenia persons indigenous to the Andean highlands had used the coca leaves growing there as a mild stimulant, mainly by chewing. Spanish conquistadores quickly prohibited use of the leaves, but it was said that coca allowed the workers in mines and elsewhere to work longer, harder, and with fewer complaints; therefore, coca leaf chewing again became acceptable.[2]

Conflicting stories about the properties of the coca leaf and its unknown active principles led to more intensive chemical investigation. Shortly before our Civil War, Albert Nieman in Austria isolated an active ingredient and named it cocaine. One of the popularizers of coca was Angelo Mariani who concocted a wine containing an extract of coca leaves. *Vin Mariani,* as the product was known, had prestigious admirers all over the Western world. Thomas Edison valued it and Pope Leo XIII awarded Mariani a gold medal.[3]

In the mid-1880s a major event changed the pattern of coca use: purified cocaine began to be produced in commercial quantities. The pharmaceutical industry had established efficient international marketing procedures. Merck and Co. produced it in Germany and exported it to the United States, where the Parke, Davis Co. was equally engaged with cocaine production, distribution and promotion.[4] The value of cocaine and its apparent harmlessness greatly encouraged not only pharmaceutical manufacturers but also medical experts who wrote essays of praise with considerable conviction. Writers not uncommonly referred to their own positive experiences with

the drug.[5] These were instances of an author going into a topic and the topic going into the author.

In this regard I cannot avoid referring to Dr. William A. Hammond, who enjoyed great credibility as a spokesman for cocaine. A professor at several medical schools and considered one of the founders of the specialty of neurology, he had been Surgeon General of the U.S. Army during the Civil War and even wrote plays and novels.[6] Dr. Hammond, an expert on the effects of cocaine by any objective criterion, could find no fault with the drug. More than that, he recommended it for common human failings—not merely for the serious problem of melancholia, but for when feeling down. He even perfected the ideal "coca wine," two grains of cocaine to a pint of wine, and drank a glass of this with his meals.

"What is true of the wine," Dr. Hammond told the Virginia Medical Society in 1887, "is more emphatically true of the active principle, cocaine." Some physicians questioned his faith in the safety of cocaine, but Dr. Hammond brushed their doubts aside. He said he was "not aware that a fatal dose of cocaine [had] yet been indicated by actual fact." Well, then, was cocaine not addictive? Not at all, replied the great neurologist. He denied "that there is such a thing as a cocaine habit, pure and simple, which the individual cannot, of his own effort, altogether arrest."[7]

Moving from the medical world to the vast public arena, we observe that cocaine use spread amid equal enthusiasm. Cocaine was the first simple remedy for a very annoying ailment, hay fever. At the time, hay fever was considered a problem of the more civilized people of the world, a sign of extreme refinement. American experts in this area proudly claimed we had more hay fever than any other nation.[8] Cocaine was adopted as the official remedy of the Hay Fever Association.[9]

Turning from the needs of those with a physical or emotional complaint to the entire population, we come to one of the most popular beverages in the world's history, Coca-Cola. As first sold at a soda fountain in 1886, Coca-Cola was a *temperance* coca beverage. The formula appears to have been an imitation of the famous French coca wines, such as *Vin Mariani,* but without alcohol. Those who feared the effects of alcohol could still obtain the benefits of the coca plant. The advertising slogans were explicit about exactly what the Coca-Cola drinker could expect. In 1890 the drink was described as "the wonderful nerve and brain tonic and remarkable therapeutic agent." In 1893 customers were urged to buy "the ideal brain tonic" and by 1899 you could learn that "Coca-Cola makes the flow of thought more easy and reasoning power more vigorous."[10] Between 1900 and 1903 the Coca-Cola company removed cocaine from the formula. The fraction of cocaine in the formula by the time it was removed was one four-hundredth per cent.[11]

When we come to the removal of cocaine from Coca-Cola we have reached a crisis in the earlier wave of cocaine use. In the first known advertisement of Coca-Cola in 1886, the proprietors proudly announced a drink "containing the properties of the wonderful Coca plant."[12] Within fifteen years cocaine had shifted from being a reason to drink Coca-Cola to being so negatively perceived that not a milligram could be present in the "pause that refreshes." Clearly a change had taken place in the public's attitude toward cocaine. By 1903 the Atlanta City Council passed an ordinance prohibiting cocaine from being dispensed at a soda fountain. In 1910 the President of the United States sent a Report to Congress that declared, "The misuse of cocaine is undoubtedly an American habit, the most threatening of the drug habits that has ever appeared in this country."[13] In 1912 the United States presided over the Hague Opium Convention which also dealt with the menace of cocaine in the treaty written there and submitted to the nations of the world.[14] In 1914 the Harrison Act was signed by President Wilson. That law, considered by its framers as the domestic

implementation of the Hague Opium Treaty, severely restricted the availability of cocaine without a physician's prescription.[15] Reviewing, then, the time-line of cocaine's introduction into America, about fifteen years passed from commercial availability to removal from a popular drink and fifteen more years until the substance was prohibited from almost all nonmedical use. Of course, cocaine continued to be used recreationally, compulsively and illegally, but the consensus among the many institutions of American society that cocaine was without any merit—except in limited medical uses as a block to nerve conduction—appears to have been the bedrock upon which a reduction in demand was built. Cocaine had disappeared in soft drinks, hay fever remedies and as an easily obtainable commodity from mail order houses. The public had grown extremely alarmed by the substance and those who used it.[16]

During the two decades after 1914 cocaine use declined until only occasionally was the drug seized and were users arrested. In 1900 cocaine was everywhere and in everything from Coca-Cola to hay fever remedies, but by 1940 cocaine use had become uncommon. By the time I took the medical school course in pharmacology in 1960, cocaine was a memory for the professors and news to the students.

The campaign against cocaine was successful, although the length of the battle was longer than those alarmed by it would have liked. The change in attitude toward cocaine, however, involved more than just the fear of cocaine's effects—causing agitation, violence and a lack of judgment. An extreme fear of cocaine's liability to create violence appears to have led some Americans to link it with other fears then prominent. These links extended beyond the murky underworld of crime and prostitution. Prior to World War I a linkage between cocaine and Blacks became a commonplace accusation. Although both blacks and whites used cocaine, the link with blacks was emphasized. One can speculate that whites who feared black hostility—and raised lynching to a peak around 1900—were happy to locate a chemical reason why blacks were hostile to civic repression.[17]

Thus the decline in demand for cocaine was not an unalloyed crusade. The fear of drugs spilled over into other areas providing, for example, in the case of Southern Blacks, a simplistic explanation for hostility.

I have dwelt on the first cocaine epidemic for two reasons: I believe the history is of particular interest now when we can see parallels between that change in attitude and the one we have lived through in the last fifteen years or so. The other reason is that I have space only to mention some of the other examples of change in attitude toward seductive chemicals, and the first cocaine epidemic is a convenient model to which these can be compared.

Morphine and other opiates have had a more gradual rise in use and a decline perhaps less precipitous than cocaine. Opiate consumption in the United States peaked in the 1890s after rising throughout the 19th century in an open market.[18] The lack of restrictions on opiates until very late in the century and the total lack of any national controls were both due to our Federal form of government as practiced in the last century, that is, a strict reservation of police power—under which antidrug activities generally operate—to the states. Opiate use, furthermore, did not fade as completely as cocaine and began a gradual rise in the 1950s, earlier than cocaine which came back about 1970.

Alcohol is perhaps the most important substance about which the United States has witnessed recurrent waves of use and alterations of attitude from positive to negative. It is important, I believe, to stress that the changes in attitude from tolerance to intolerance are not just to be found in the decades leading up to national prohibition in 1920 and the backlash to prohibition that began after 1933. This view too easily makes of the antialcohol movement and Prohibition a mere aberration in our social

history, a peculiar event that can safely be forgotten. As I have suggested in regard to our first cocaine epidemic, we can easily forget antidrug campaigns, but it is to our loss that we do so.

The first antialcohol movement which led to widespread prohibition in the United States began early in the 19th century. Alcohol had been thought a tonic, a remedy for disease and an aid to physical labor. Record consumption of distilled spirits about 1830 worried many Americans who noticed that alcohol in large amounts did not seem to match the claims for it. Consumption levels declined and about a dozen states enacted prohibitory laws.[19]

Perhaps the Civil War absorbed these reforming energies, but whatever the reason observance of the laws declined in the 1860s and once again consumption climbed. In the 1890s the Anti-Saloon League was formed to combat the most offensive expression of alcohol, the saloon.[20] Gradually the focus of antagonism spread from the saloon to alcohol itself, just as antagonism to distilled spirits in the 1830s gradually grew to encompass all forms of alcohol. By January 1919 the thirty-sixth state had ratified the 18th Amendment to the Constitution and a year later we entered national prohibition. In the 1920s we hit the lowest level of alcohol consumption in our nation's history.[21]

The eventual repeal of Prohibition stemmed from a combination of factors. First, unlike cocaine, there was a cultural acceptance of alcohol among tens of millions of Americans. Although the amount consumed was greatly reduced, the use of alcohol could not be extinguished to the degree that had been accomplished with smoking opium, with other opiates and with cocaine. Then the onset of the Depression made Repeal an attractive stimulation of employment and needed revenue.[22] Repeal, however, came with a backlash, a weariness with talk of controlling alcohol and alcohol-related problems. Fifty years would have to pass before popular movements like Remove Intoxicated Drivers (RID) and Mothers Against Drunk Drivers (MADD) could again raise questions about alcohol without being apologetic or defensive.

Now we are, I believe, entering a new temperance era, a growing awareness of the negative side of alcohol.[23] Several crucial elements of earlier temperance movements can be seen. First, an aspect of alcohol's social impact abhorrent both to drinkers and to abstainers has been identified and broadcast: I refer to the drunk driving problem. Second, the multiple, distinctive forms of alcohol, spirits, wine and beer are collapsing into one significant common denominator: they are all alcohol and the other characteristics are irrelevant. Third, alcohol is moving from a substance helpful, or at least harmless, when taken in moderation toward being a poison, damaging to the extent that it is consumed. Significant factors in this last transformation are studies on the Fetal Alcohol Syndrome and, more recently, warnings against the male partner's consumption of alcohol near conception.[24]

The battle against alcohol and the other chemicals I've mentioned easily become moral contests in which no quarter can be given to the hated enemy. The path toward prohibition is logical and ethical to many combatants against dangerous substances. If we are entering another era of temperance, we can greatly benefit from knowledge of similar past trends. History does not, of course, prescribe our future actions, but it can cause us to reflect on our efforts and their possible outcomes, to expand the factors we employ in analysis and to take into keen consideration the long-term consequences of victory.

One of the saddest aspects of Prohibition was the backlash that inhibited direct and frank consideration of the alcohol problem for half a century afterward. The task of persons deeply concerned about the impact of alcohol and other chemicals on the health of the born and unborn is to consider how to create lasting changes in behavior that will not be subject to the wide swings in attitude that have characterized past