MOLECULES REVISITED

In response to the "Molecular Madness" article in Issue 92, Ivan Valentic from Bistrica, Slovenia writes:

"Maybe you have already realized that formulac for tryptamines in your issue number 92 issue are almost all wrong, and some substances, eg tryptophan, are not even tryptamines! Please consult the enclosed table compiled by A. Shulgin, or him personally.

Sincerely, Ivan Valentic

Well, let's go over some of the things I was going to show you this issue. First off, the molecules were just fine as shown, it's just that there are a million different ways to show these things. Sure, in Shulgin's "Structure-Activity Relationships of Classic Hallucinogens and their Analogues" (the paper supplied by Ivan) the structure for DMT looks different. In fact, it's upside down! Well, that's OK, in these simple models of complex mechanisms the important things are the relationships of the parts to the whole, not necessarily their orientation in 3-D space. (Ike stated in that previous article, no attempt was made at showing dimensions in space, or for that matter, any "proper" orientation on 2-D paper.) The way the molecules were arranged in that previous article was to show similarities in an arbitrary "family" of analogues. That's why "Tryptophan" was in with the Tryptamines, just to show the similarities. Again, these were designed to show similar trails within families.

But what about similarities that exist between the families? You may have noticed that LSD has a sort of "trypamine" skeleton inside of it. This is the indole nucleus, a characteristic of many of the larger family of chemicals that both LSD and tryptamines belong to. Is there any similarity, then, to the amphetamines? Well, if you really use your imagination there is. Can these similarities in structure be used to predict the activity of these compounds? That is indeed the 6 million dollar question. One that is perhaps still unanswered.

The bottom line is that we still don't understand how particular substances within LSD work. Researchers can look at a lot of biochemical and electrophysiological effects in animals, agonist activity at 5HT[1A] receptors causing decreased serotonin release (the "preyed" or "anti-serotonin" hypothesis), partial agonist at post-synaptic serotonin receptors, some interaction with dopamine and other receptors, but no one can come close to putting together these disparate facts into an explanation that accounts for the subjective effects in humans. Ah, but that is an entirely different part of the problem. We do not know which groups of chemicals cause these effects and attempts have been made to understand what if anything they have in common.

Solomon Snyder and Elliot Richelson in their pioneering presentation "Steric Models of Drugs Predicting Psychiatric Activity" try to tackle the problem of explaining these relationships. (Cox, incidentally, this paper was presented at the same meeting, at UCI in 1969, a workshop organized by the Pharmacological Research Branch of National Institute of Mental Health) that Dr. Shulgin presented "Chemistry and Psychotropic Activity: Structure-Activity Relationships of the Psychotomimetics" and in fact first defined the term "Psychotomimetic." See the side bar.) Snyder and Richelson dig deep and look at the 3D relationships of molecular structures. If you think the 2D molecules as presented last time didn't look "right" just check out these models. And again, they're models - actually crude stick molecule figures, that attempt to present 3D relationships on a 2D surface. We now know that temporal considerations must also be accounted for, which only makes the models more and more complex. What Snyder and Richelson have done is to show how these models might arrange themselves in space, according to their charges, bonding characteristics and electronic configurations. Their hypothesis is that within steric classes of compounds, pharmacological potency was related closely to the energy of the highest occupied molecular orbital (HOMO), an index of the electron donating capacity of the resonating electrons of the molecule. They noted that models of known psychotropic compounds of three major classes [tryptamines, phenethylamines and amphetamines] can all approximate a conformation simulating in part the major ring structures in LSD.

In the more potent derivatives, certain structural features might permit the stabilization of the hypothetical "active" conformation, perhaps enabling the prediction of psychotropic activity. Basically, the stabilizing and thus potentiating action is demonstrated in the three figures. LSD at the top is by far the more potent configuration that includes plenty of "stabilizing" atoms. The electrons in the outer "D" ring can resonate with the electrons of the indole ring to produce a more energetic HOMO. This arrangement is of a higher energy order than in the tryptamines, which is reflected in their relative psychotropic potency. The most potent tryptamines, (represented here by psilocin, the active principle in magic mushrooms) are the ones that can approximate the "C" ring of LSD. With psilocin, an amine group is attracted to a hydroxyl group and physically permits hydrogen bonding between the two groups, thus stabilizing an eight membered ring which in 3 dimensions resembles the "C" ring of LSD. DMT lacks this arrangement and is far less potent than psilocin or tryptamine, is by far the least potent of the three in this discussion. But it is active. The side chain of the phenethylamine forms down toward the ring, thus resembling the indole nucleus (rings "A" and "B" of LSD) and providing the stabilization needed for a more energetic HOMO.

We have to remember that this is a model that tries to explain any activity at all. There are a lot of other things that effect potency as well - enzymatic activity and metabolism are also very specific to molecular structure. On the other hand, you try to explain why crack babies are born "addicted" to drugs. Many of you who have experienced addiction know that you can pretty much kick that monkey off your back in less than a week. The real problem is getting the desire to get high. Well, that little baby ain't gonna take the rent money to cop some dope! So after a week or so, that kid should be clean. Well, that's what I figured. But there's more to it. You have to look at the mechanisms of addiction to really see what's going on.

Cocaine (any way you choose; blow, crack, freebase, etc) disrupts the normal balance of at least three essential neurotransmitter systems: noradrenergic, dopaminergic, and serotonergic. Serotonin is responsible for regulation of sleep. Cocaine tends to depress neurotransmission of serotonin and can lead to insomnia, irritability and general paranoia. The general purpose of Noradrenaline (nor-adrenaline) is to prop the body for emergency. Cocaine greatly increases its retransmission and producing increased heart rate, higher blood pressure etc. Continued levels of this intense stimulus can lead to respiratory failure and cardiac arrest. Dopamine, then, is where the addiction problem comes from.

Dopamine is responsible for what we feel as euphoria and pleasure. In general, as our bodies use these neurotransmitters, they are absorbed and recycled again and again. Cocaine acts to block the reabsorption of dopamine, this prolongs its activity in the brain synapses as causing a rush of euphoria. Then your dopamine is, however, metabolized and excreted before it can be recycled. As you deplete your supply of available dopamine, your craving for cocaine goes up and up. Your ability to experience pleasure is dramatically altered. Your body's ability to naturally feel good is impaired and the only way to even feel alright is to use more cocaine to block the reabsorption of what little dopamine may still be left in your body. Some researchers believe that chronic use of cocaine may cause permanent depletion of these neurotransmitters and irreparable damage to the brains dopamine receptors.

In contrast, heroin works on a class of neurotransmitters called endorphins ("endogenous morphine"). Endorphins are the body's natural way of dealing with stress, a situation very similar to one with dopamine. When you use heroin you flood your body with endorphins. A superior sense of well being and calm results. Your body is fooled and feels that its natural production of endorphins is redundant, and shuts down. In due time the body is deprived of the endorphins, and heroin becomes a must. Without you it start to feel every pain that used to be so conveniently covered up. Your back starts aching first, then every joint in your body - no endorphins to lubricate the pain away from everything that moves. The opiate is a poison, don't seem to cause a permanent depletion of these neurotransmitters. Your body eventually reacts to the pain, with its own defense system - production of endorphins.

Well, I strayed from the topic there a little. What does this have to do with Crack Babies? I think this is probably intellect of permanent dopamine depletion from their mothers? Most researchers think not. In fact, idea of "Crack Babies" may be nothing more than a myth, as you will read shortly.

The real dangers with cocaine use for the average person are most likely not the long term depletion of dopamine. The over-stimulation factor associated with heart failure is a serious concern, as is the effects of smoking the hot and harsh vapors of crack or the irritation of the cocaine "hydrochloride" salt to your nasal membranes. The biggest danger is the most common one, getting busted by the police and spending the rest of your life on drugs. I was in a small city in South Carolina, a woman recently got a life sentence for selling an undercover cop $40 worth of cocaine.

But you're gonna do it anyway, I know how you are. I knew this guy once that would go on and on about the advantages of smoking freebase over snorting powder - basically pumping the fact that it is more effective when smoked and has a neutral pH factor, not an acid salt like cocaine hydrochloride. I mean, what is the hell is the difference between the powder, the freebase and crack. Well, let me explain.

Basically, "freebase" cocaine is what you typically know as the powder form of "cocaine hydrochloride" separated from its acid radical. You simply remove the "hydrochloride" part.
There's the question of what's going on with the text. It seems to be discussing ways to freebase cocaine and the effects of doing so, but the text is disorganized and difficult to understand. There are references to chemicals and pharmaceuticals, but the overall coherence is lacking. It appears to be a mixture of technical and informal language, possibly from different sources or draft versions of a document. The text doesn't follow a clear structure and is hard to follow. It seems to be a page from a book or a document, but the content is not clear or coherent.
Another researcher who has taken a responsible second look at the “crack baby” syndrome is Claire Coles of Emory University. She believes these children, labeled by their drug of origin, are in fact “often victims of gross neglect, not brain damage.”

The worst damage that drugs may do is to the world a child inhabits after birth. Coles has a collection of horror stories about children growing up neglected, especially by cocaine addicts. One “crack kid” who couldn’t concentrate in class was in fact hungry. Another poorly developed “crack baby” was being “raised” by a 5-year-old sister.

The myth of the “crack baby” became a media hit. Coles believes, because “crack is exotic and happening mostly to marginal populations among ‘bad people’ who are not like us,” it is easier to think about crack than alcohol or tobacco. There is more than a touch of racism in the attention.

But perhaps the worst effect of this distortion is the sense of hopelessness dispensed with the title “crack kid.” Hopelessness is on the part of mothers, teachers, and even the children themselves. As Coles warns, “if a child comes to kindergarten with that label, they are dead. They are very likely to fulfills the worst prophecies.

So, no more convenient and empty names. The children whose mothers used cocaine are neither universally nor permanently lazy nor uniquely damaged.

The so-called “crack kids” are just a portion of our growing population of children in deep trouble. They are only children, like so many others, growing up with a tremendous mix of needs and nurture’s woes.

If you need a label, call them kids who need help.

- Ellen Goodman is a Globe columnist.

"SMOKING OUT COCAINE’S IN UTERO IMPACT" (Science-News November 1991)

Despite many reports of cocaine’s effects on the developing fetus, scientists lack definitive evidence specifically linking cocaine to adverse reproductive effects (SN: 9/7/91, p.152).

Using a powerful statistical technique, a Canadian research team has found that cocaine use by itself causes very few problems during pregnancy.

- Sidney Koren of the University of Toronto and his colleagues identified 20 previously published cocaine studies that involved pregnant women and yielded mixed results.

Those studies often relied on small samples of cocaine users, a problem that limited each study’s statistical power.

To home in on cocaine’s reproductive risks, this team turned to a newly called meta-analysis, which statisticians use to assess data by pooling a number of similar studies. Koren and his colleagues identified women in the 20 studies who used cocaine during pregnancy but did not use other illicit drugs or alcohol, and compared them with those who reported no drug or alcohol use during pregnancy. They found no statistical link between prenatal cocaine use and premature delivery, low birthweight or congenital heart defects in babies — problems often thought to result from cocaine.

The meta-analysis suggests that confounding factors — such as other drugs, alcohol and smoking — may account for the fetal growth retardation or prematurity, commonly ascribed to cocaine, the researchers assert in the October “Teratology.”

Koren says women who use cocaine tend to smoke more cigarettes than women who use other illicit drugs and are more likely to drink alcohol and take additional drugs.

The meta-analysis did not say the babies were born addicted, or afflicted. He did not say which mothers used cocaine daily and which used marijuana one weekend. He said: some quantity of some illegal drugs was used during pregnancy. Then Chasnoff did the arithmetic. If there was drug exposure even 10 percent of the 3.75 million births in the U.S. annually, that would be 375,000 babies.

"That," Chasnoff said, "is as far as it went." (goes on to detail how William Bennett used this study to show that there were 375,000 crack babies in the U.S./year.)

BIAS AGAINST THE NULL HYPOTHESIS: THE REPRODUCTIVE HAZARDS OF COCAINE

by Korin G., Graham K., Shear H., Enarson T.
Department of Pediatrics, University of Toronto.

To examine whether studies showing no adverse effects of cocaine in pregnancy have a different likelihood of being accepted for publication than those showing adverse effects, the authors performed a meta-analysis of all abstracts submitted to the Society of Pediatric Research between 1980 and 1989.

They found that studies showing no adverse effects were more likely to be accepted for publication than those showing adverse effects (65% vs. 58%). This difference was significant. Studies showing adverse effects were more likely to be rejected than studies showing no adverse effects (23% vs. 11%).

The authors concluded that the bias against the null hypothesis may lead to distorted estimation of the teratogenic risk of cocaine, and thus cause women to terminate their pregnancy unnecessarily.

RELATIONSHIP BETWEEN GESTATIONAL COCAINE USE AND PREGNANCY OUTCOME: A META-ANALYSIS

by Luliger B., Graham K., Enarson T.R., Koren G.
Department of Pediatrics, Hospital for Sick Children, Toronto.
Despite a growing number of studies that have investigated the reproductive effects of maternal cocaine use, a homogeneous picture of findings has not been established and there is little consensus on the adverse effects of the drug. We used meta-analysis to evaluate the reproductive risks of cocaine. We reviewed 45 scientific papers published in English that deal with effects of cocaine use during pregnancy on pregnancy outcomes in humans, and identified 20 papers eligible for meta-analysis (coca use in pregnancy, pregnancy outcome, and cocaine use in humans, original work, cohort or case control studies, control group present, English language). Our analysis revealed that the adverse reproductive effects could be shown to be significantly associated with cocaine use by polydrug users when compared to control groups of polydrug users not using cocaine (0.37; CI 0.0-0.75). When the control groups consisted of no drug users, polydrug users abusing cocaine had a higher risk for spontaneous abortions (odds ratio: 10.5; CI 11.7-94.1). Similarly, comparison of users of cocaine alone or no drug users revealed a higher risk for in utero death, in addition to gynecological tract malformations. Analysis of continuous variables (head circumference, gestational age, birth weight and length) revealed that the effect size was dependent upon the nature of the comparison. Comparison of cocaine users to no drug users consistently yielded a medium effect size (Cohen’s d between 0.50 and 0.85), while comparison of polydrug/cocaine users to polydrug/no cocaine users provided effect sizes small to nonexistent (0.06-0.37). These discrepancies suggest that a variety of adverse reproductive effects commonly quoted to be associated with maternal use of cocaine may be caused by confounding factors clustering in cocaine users.

COCAIN/POLYDRUG USE IN PREGNANCY: TWO-YEAR FOLLOW-UP
by Chasnoff I.J., Griffith D.R., Freier C., Murray J.,
Department of Pediatrics, Northwestern University Medical School, Chicago, IL, Pediatrics 1992
February 2:284-5 Feb 1992
The impact of cocaine on pregnancy and neonatal outcome has been well documented over the past few years, but little information regarding long-term outcome of the passively exposed infants has been available. In the present study, the 2-year growth and developmental outcome for three groups of infants is presented: group 1 infants exposed to cocaine and/or alcohol (n = 106), group 2 infants exposed to marijuana and/or alcohol but no cocaine (n = 40), and group 3 infants exposed to no drugs during pregnancy. All three groups were similar in racial and demographic characteristics and received prenatal care through a community-based drug treatment and follow-up program for addicted pregnant women and their infants. The group 1 infants demonstrated significant decreases in birth weight, length, and head circumference when compared to control infants. The group 2 infants exhibited only decreased head circumference at birth. Head size in the two drug-exposed groups remained significantly smaller than in control infants through 2 years of age. On the Bayley Scales of Infant Development, mean developmental scores of the two groups of drug-exposed infants did not vary significantly from the control group, although an interaction of proportion of group 1 and 2 infants scored greater than two standard deviations below the standardized mean score on both the Mental Developmental Index and the Psychomotor Developmental Index compared to the control infants. Cocaine exposure was found to be the single best predictor of head circumference. (Note that Dr. I.R. Chasnoff was responsible for a very great deal of the original cocaine-baby research in the mid 1980s.)

PREGNANCY OUTCOME FOLLOWING FIRST TRIMESTER EXPOSURE TO COCAINE IN SOCIAL USERS IN TORONTO, CANADA
by Graham K., Dimitraides D., Pellegrini E., Koren G.
Department of Clinical Pharmacology and Toxicology Research Institute, Toronto, Ontario, Canada. Vet Hum Toxicol 1989 Apr;31(2):143-8, 1989 Apr 1989 Vet Hum Toxicol, PG.143-8
Studies of drug-dependent women reveal high rates of IUGR and other fetal effects of cocaine. However, no data are available on the effect of the chemical in social users who discontinue cocaine upon realizing they are pregnant. We report the results of the first phase of a prospective study examining the outcome of pregnancy in women seeking counseling from the Motherisk Program in Toronto. Of 25 women seen in our clinic for first trimester cocaine exposure, 92% reported use of 10 g of cocaine and 36% report marijuana use. Other illicit drug use was rare—cigarette and alcohol use was common. The study group did not experience adverse pregnancy outcome above the rate expected in the general population. There were 23 single births 1 twin of twins, and 1 spontaneous abortion. Birth weight and gestation were within normal limits. Only 1 child had a major malformation, syndactyly. Infants' development was within normal limits, as measured by developmental milestones. All children are scheduled for assessment using the Bayley Scales of Infant Development. The results of the BSID will be compared to results from a cannabis-exposed control group and a no-drug control group.

LACK OF EFFECT OF MATERNAL COCAINE ADMINISTRATION ON HYOMETRICAL ELECTROLYTES IN MAMMAL PLASMA OXYTOCIN CONCENTRATIONS, MALFORMATIONS IN PREGNANT SHEEP AT 124-145 DAYS' GESTATIONAL AGE
COCAIN IN PREGNANCY: ANALYSIS OF FETAL RISK
by Koren G., Graham K.
Department of Pediatrics & Research Institute, Hospital for Sick Children, Toronto, Ontario, Canada Vet Hum Toxicol 1992 Jun 34(3): P 283-4
During the last decade there has been a substantial increase in the recreational use of cocaine in young adults and partially there has been an increase in its use by pregnant women. We analyzed all published data on cocaine use in pregnancy and found that for most endpoints studied (e.g., prematurity, head circumference), there were many studies showing effects and many showing no effects. Upon meta-analysis, most of the effects could not be shown significantly when compared to control groups. In a prospective study in Toronto, babies exposed to cocaine during the first trimester only had Bayley scores at 18 mo of life that were identical to unexposed babies or to those exposed to cannabinoids. Motherisk presently counsels women who discontinue cocaine use in the first trimester of pregnancy that there is no increased developmental risk for the baby.

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