Bloom Caramazza Dennett Gallistel Kosslyn Newsome Pinker Posner Raichle Tulving

Conversations in the Cognitive Neurosciences

edited by Michael S. Gazzaniga

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Preface

Science is hard work. It is also an endeavor that is inherently cautious and measured. All too often what seems to be a clear answer to a problem in one context surfaces as a poor interpretation in another. Scientists know this and because of this fact they usually try to stay close to their data when discussing their results in scholarly publications. That is how it should be.

At the same time, the stuff that drives scientists into their laboratories instead of onto the golf links is the passion to answer questions, hopefully important questions, about the nature of nature. Getting a fix on important questions and how to think about them from an experimental point of view is what scientists talk about, sometimes endlessly. It is those conversations that thrill and motivate. And yet, most of these exchanges are lost rather than being captured for the student.

One evening several years ago we were ending one of our dinner parties that my wife and I host when a speaker comes to town. We love these evenings, as they represent a time when we can pursue a topic with our guests with all gloves off. After one such occasion a friend remarked that it was a pity not to have the conversations somehow available for

others. It had been a particularly lively evening. It was then I thought of doing interviews with famous scientists for the *Journal of Cognitive Neuroscience*.

Over the past few years I have carried out a number of interviews on topics that range from molecular mechanisms to philosophical issues. Each interview has been managed on e-mail, the new glue that binds us all. Overall they take about 10 days to complete, after which the participant and I review the product and make small adjustments. Most of it, however, is not changed a whit, and out of that comes a spontaneity and zip from the interviewees that makes for good reading and gives great insight into the way they think.

The *Journal* will continue to do these interviews. We decided, however, we were at a point where they should be brought together as a unit for the public to enjoy.

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Floyd E. Bloom

Floyd E. Bloom, M.D., is Chairman of the Department of Neuropharmacology at The Scripps Research Institute (our new name after July 1, 1991). He was educated at Southern Methodist University and Washington University School of Medicine, with postgraduate training at Barnes Hospital in St. Louis, and the National Institute of Mental Health (NIMH). He held faculty positions at Yale University before returning to the NIMH to head the Section on Cytochemical Neuropharmacology, the Laboratory of Neuropharmacology, and the Division of Special Mental Health Research. Before his current affiliation with Scripps, he headed the Center for Behavioral Neurobiology at the Salk Institute.

Bloom's interests are wide-ranging, but all deal with a desire to understand the brain's operations in molecular and cellular terms, both normally and in pathological circumstances, and to devise means to restore healthful operations. His current efforts include studies on the central nervous system's reactions to alcohol, the mechanisms of AIDS dementia, and the molecular basis for neutral specificity. He is a member of the National Academy of Sciences, the Institute of Medicine, the American Philosophical Society, the Royal Swedish Academy of Sciences, past President of the Society for Neurosciences and the American College of Neuro-Psychopharmacology, and Past-President of the Research Society on Alcoholism.

MG: The problem of drug addiction consumes much of our culture's energy. There are those who feel that the calm scientific analysis of the problem is not possible, mainly because hard science has little to say about the issue. As a neurobiologist, how do you view the problem and where does neurobiology fit into the current discussions?

FEB: From the perspective of a neurobiologist, all drug actions, including those of abused drugs, are based on well-characterized cellular sites and molecular mechanisms of action. The changes in cellular activity produced by these drugs lead to changes in sensory processing, motivation, attention, and arousal. Pharmacology attributes reinforcing responses, or "pleasure," to the complex set of drug-derived internal cues. All of that integrates into the perceived drug response that can motivate subsequent drug seeking behaviors. There are two more phases of the drug-brain interaction that need to be noted: (1) the adaptations that may lead to tolerance to the information-processing confusion induced by the drug effects, and (2) the subsequent long-term craving for the drug. If we are ever to find ways to help addicted humans beat their long-term problem, we must understand far more thoroughly the nature of what brain systems (transmitters, cells, and circuits) underlie drug craving. At the present we know a lot of transmitters that mediate the acute drug reinforcement of opiates and psychostimulants, but really nothing solid about the events that are taking place when a person remembers the initial reinforcing events of a previous drug-taking trial and tries to deal with the decision to use, or not to use.

MG: But, is that doable? After all, one assumes drugs are tweaking the reinforcement systems of the brain, the same reinforcement systems that are essential for any sense of pleasure, or reinforcement. If drugs were developed that

blocked action on these reinforcement systems, would that not block normal mechanisms for reinforcement as well?

FEB: Our understanding of "reinforcement" mechanisms has also progressed a great deal, and it is probably no longer accurate to consider there to be one and only one such system. Insofar as these major drug types are concerned, there are some shared features of "pleasure" that may employ a common underlying general reinforcement, but the primary avenues for the initiation of the reinforcement perception arise uniquely for the drug. In my interpretation, the ways in which opiates initiate their form of pleasure are unique from those "tweaked" by psychostimulants of the drugs exemplified by cocaine, amphetamine, and congeners, and those are still separate from the ways in which caffeine or nicotine do their trick. Beyond the primary site and mechanisms of initial response, the other main place in which I believe there is a feasible approach is the remembrance of the pleasured response, which together with its environmentally dependent associations creates the craving scenario. In my concept of this scene, the present data provide opportunities to separate drug-induced reinforcement from reinforcement generally, and to deal with drug craving without canceling human memory. There is also some hope that the piece in the middle may also be manipulatable: George Koob and his colleagues presented data at the 1991 Neuroscience meeting that some dopamine blockers can interrupt cocaine reinforcement and not food reinforcement, and vice versa.

MG: That is a very strong and intriguing claim. It does suggest therapies might be developed to inhibit the reinforcing properties of particular agents. However, are we not left with the larger problem of individual needs? In other words, isn't it the case the user is still seeking ways to increase their sense of self by being reinforced by something in these artificial

ways? If you find a way of blocking their highs from cocaine, won't they find their highs from alcohol? It is known that when one cures a cocaine addict, they generally move the person over into the alcoholism category.

FEB: There is no denying the clinical evidence that for many people on their way into the drug seeking pattern there is progression from cigarettes and alcohol to other more powerful uppers and downers. The primary pharmacology here is more or less drug selective, and the transitions and motivations to go on are probably unique to individuals in terms of their propensities for risk-taking, harm avoidance, or desire for internal rewards or external rewards, such as peer pressure and acceptance. Robert Cloninger at Washington University has found these "personality" qualities assessed in young boys can accurately predict their drug taking status fifteen years later.

Moving out of illegal drugs back to socially approved (and taxable) drugs may have a reverse sequence, although those are not data that I know about. However, the more fundamental answer to your question is that in my view the ultimate answer for a person who has become drug dependent is not another drug, at least in the long run, but rather the identification of the internally perceived problems that drove them to be drug seekers rather than accepting natural rewards (food, sex, money, fame, etc.).

The recent findings of a high incidence of serious mental illness in drug abusers and vice versa suggest that there may be significant mixtures of psychopathology, especially depression, in drug users. The self-termed normal user is in essence walking a very precarious tightrope in trying to "use" drugs recreationally without entering the domain of tolerance and dependence, and the false belief that they can stop whenever they want to.

The admittedly dependent person has already crossed over, and is the person toward whom the current treatment emphasis has been directed; drying them out, and then trying to find better ways to defer long-term recidivism within the environmental situation that spawned their dependency. No therapy could be considered as either ideal or even practical, if it destroyed the subject's ability to have internal reinforcement; such a state of anhedonia is in fact a major symptom in some types of schizophrenia.

MG: OK, but in a larger sense what we are trying to get at here is a science-society interaction issue. The question is whether, and if so, how neuroscience research might help evaluate the society cost effectiveness of the amounts the government is spending to reduce the supply of illegal recreational drugs. If, as the NIDA data say, only 2 percent or so of Americans "deal" or use illicit drugs regularly, is it possible to figure out which of the many more one-time trial users are likely to have a real problem with continued use, and which are likely to go on about their entertainment business without becoming addicted?

FEB: Yes, there are signs that we can predict which of a dozen individuals, when given the chance to take all the intravenous amphetamine they want, will go for it, and which, after a few buzzes, will say no thanks. The answers that impress me come from Michael LeMoal at the University of Bordeaux, who noticed that only about half of the rats who learned to give themselves amphetamine by poking their noses through specially marked holes in their test cage showed the feature of "sensitization" in which the same drug dose on subsequent days produces greater and greater locomotor activation. In trying to figure out what was different about the ones who did and did not show this effect, he

noticed that when the rats were prescreened for their willingness to explore a new cage environment, and for their adrenal corticosteroid secretion patterns in this novel test cage, those who went on to show the sensitization response were more vigorous explorers and showed higher steroid secretion peaks than those who did not. The low steroid secretors–low explorers also showed less and less interest in getting their amphetamine, and so after five or six days, they just ignored the opportunity to take the drug, while the high secretors–high explorers were increasing their doses, getting more excited, and getting more drug to get even more excited. Mary Jeanne Kreek at Rockefeller has noticed similar findings in their cocaine abusers.

This could be interpreted in several ways, many of which are testable: high environmental stress might elevate one's secretion patterns, increase exploration (looking for a way out), and the double enhancement sensitizes the reward system to a hit of psychostimulant, which then mutually accelerates the whole cycle. Some may be genetically prone to being hyperreactors (or hypo); or concurrent mental illness, like depression, may emulate parts of the endocrine drive, and increase the risk of drug effects leading to dependency in individuals who might otherwise be able to decide not to use again and again.

MG: Yes, but again, are we dealing with such a complex set of issues—mental illnesses, sociopaths, homelessness, poverty, and ill-defined aspirations—that it is impossible to think of a simple biomedical remedy?

FEB: This is not unlike one of the earlier questions, but maybe we can approach it from another angle. There are three parts to the "drugs against drugs of abuse" conundrum: (1) finding drugs that will prevent the drug's initial

reinforcement action to reduce the probability that casual users would find them rewarding, or that repeated abusers would continue if there was no reward, (2) in the case of heroin abusers, nicotine smokers, and alcoholics where drug-free periods immediately after periods of high-frequency use lead to immediate withdrawal symptoms, treatment with partial agonists would reduce the negative reward of the withdrawal, and unless the system could adapt to the drug-free state quickly, would substitute a no-reward drug for a reward-driven drug, and (3) drugs that could prevent long-term recidivism, long after the last drug use, often precipitated by subconscious environmental or social cues. Number 1 is constrained by the fact that while such antagonists now exist, taking them routinely, or adding them to the drinking water to reduce accidental exposure and reward carries longer term health risk (such as a parkinsonian-like disorder if taking antidopamine drugs) as well as the possibility of leading to anhedonic zombies, since the natural reward systems have long-term survival value. The other two are constrained by the issue of voluntary compliance, which is at best irregular until the individual with the problem decides for themselves to deal with it seriously, and for a long enough period of dedicated dealing that they can get straight and stay straight.

While we know a lot about the kinds of transmitters and actions that go into the drug-induced rewards for opiates, psychostimulants, nicotine, and to some degree ethanol, we know nothing at all about the other drugs yet (PCP, THC, LSD), nor about the longer term craving effect and its ability to be triggered by environmental cues. I think understanding those chemical circuits could augment the future anti-drug treatment armamentarium.

MG: Can neuroscience illuminate the real cost to the drug victim, which is not necessarily the long-term loss of neurons as with chronic excessive ethanol consumption, or the loss of life due to cancer or cardiovascular disease with smoking, but rather the retreat into the drugged state that robs them of their human intellect? Here we are talking about the subset of addicts that is not otherwise mentally disturbed.

FEB: This is not something that I can speak to from my research reading, but I am aware that the social caste system in India has, to some degree, been maintained by the use of bhang as a reward; it is a hashish-like beverage that keeps the workers satisfied with not very much monetary reward, and in a sort of endless semi-stupor; this is not a lot different than the cholinergic stupor of the zombies, or the work-harder-for-your-coca-leaves approaches in the Caribbean and South America. Sure, there are a few people whose ability to create art and fiction while on drugs is well documented, and even a few physicians with well-documented habits while still being physicians. But the odds seem to be quite against this safe-status passage as Goldstein and Kalant pointed out in their *Science* paper last year.

MG: But that is not true, according to NIDA's own statistics. Most people do walk away from drug use. Remember, for every 100 people who try drugs only two stay with it.

FEB: I think we have to distinguish between those who really tried it only once or twice and walked away, and those who try a pattern of frequent use under the belief that they can "quit any time they want to." As I read Goldstein and Kalant, there is reason to doubt the accuracy of the reports on walking away, added to which the longer one uses the less accurate one's own perceptions and drug-quitting abilities may become. As drug-use frequency increases, the brain will