



## Part 2: Clinical Pathways

### A medical model for “Reward Deficiency Syndrome”: clinical significance of genetic dopamine deficiencies

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The discovery of the association of dopamine (DA) deficits, observed for a number of addictive behaviors, including alcoholism, cocaine addiction, carbohydrate bingeing behavior, and nicotine dependency, has wide ramifications because, fundamentally, addictive behaviors contribute greatly to the development of heart disease, cancer, AIDS, and the overall use of medical services. While it is well known that drugs of abuse cause a short term fix of hypodopaminergic brain function via preferential neuronal release of DA in meso-limbic “reward sites”, the goal of the clinical practioner is to bring about a long-term life style change. While we are cognizant about the potential of identifying multiple genes (Polygenic) which contribute to psychavtive seeking behavior, this presentation will focus on dopamine deficiencies. Genetic studies point toward DA deficiencies which can significantly impact on the electrical rhythm of the human brain with implications resulting in schizoid behavior (isolation), avoidant behavior (social phobias), and anti-social behavior (criminal and violent behaviors). Further implications of the “reward deficiency Syndrome” include learning impairments (AD/HD) and psychiatric sequelae such as bipolar depression. An emerging model includes electrophysiological mapping, and potential gene testing, pharmaceutical and neutraceutical intervention, as well as a number of alternative approaches including neurofeedback, auricular therapy, subluxation (chiropractic), cranial stimulation and long acting medical treatments (Naltrexone, Methodone, Vaccines ets). Clinics that are prepared to treat the internal medicine, neurological, psychological and spirtual ramifications presented by individuals with “Reward deficiency Syndrome”, using the full armamentarium currently at our disposal and more to be discovered, will deliver more long-term effective healthcare for the victims of simple “polygenic” molecular variation.

### “Reward Deficiency Syndrome (RDS)”, and especially substance use disorder: global problem/global solutions

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SUBSTANCE USE DISORDER (drug abuse and addiction), a behavioral sub-type of RDS, is a global problem that calls for global solutions. Smith and Seymour discuss the development of drug abuse in terms of an increasing international drug accessibility that feeds the equation: heredity + environment = addiction. Today, the spread of abusable psychoactive drugs knows no boundaries and all populations are subject to abuse and

addiction. Having stated the problem, the authors proceed to a discussion of what is being done to raise awareness and to disseminate information on current research and practice, providing useful inferences and actual procedures from culture to culture throughout the world. Although addiction in and of itself may be essentially the same phenomenon everywhere, the disease and its treatments function within cultural contexts. As a result, a treatment approach developed in New York may not work in Addis Ababa, and a public health approach that is promising in Tokyo may be inappropriate in Sydney. Experience, however, can be shared and inferences made that increase the prognosis for effectiveness. Thus, communication and the exchange of information are critical tools in the struggle against abuse and addiction. The role of printed journals, the increasing utilization of electronic media, such as the International Addictions Infoline and other online information sources, and communications and organizations that further the spread of information are highlighted. Specific organizations such as the International Council on Alcohol and Addictions (ICAA), International Society on Addiction Medicine (ISAM) and the new International Society of Addiction Journal Editors (ISAJE) and their activities in promoting the global exchange of information are discussed. Specific examples of combining clinical, quantitative, qualitative specific to biogenetic research and practice and the reporting of these in the world scientific media are presented. The authors believe that this exchange of information will ultimately lead to a unified approach specific to diagnosis and the physiological aspects of RDS, especially for drug abuse and addiction, but each culture will dictate program individuality.

### Pre-Clinical Studies with the Cocaine Vaccine IPC-1010

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A series of studies assessed the pre-clinical effectiveness of the cocaine vaccine IPC-1010 on cocaine self-administration behavior. The objectives were fourfold: (1) to determine if changes in cocaine self-administration were related to antibody level; (2) how antibody level affected self-administration of different cocaine doses; (3) if exposure to cocaine during the immunization period would influence the ability of the vaccine to induce antibodies and block cocaine self-administration; and (4) if antibody-induced reductions in cocaine self-administration were behaviorally specific. Experiments were conducted in rats trained to self-administer 1mg/kg/infusion cocaine according to a FI-5(FR-5: S) second-order schedule of drug delivery. Results showed that a minimum serum antibody level, estimated to be between 0.05 and 0.1 mg/ml, was needed to reduce drug-seeking behavior and drug intake. Antagonism of cocaine self-administration after immunization was evident across a range of cocaine doses and was only apparent in rats whose serum antibody levels exceeded this minimum. Furthermore, there was no evidence that the antagonism was surmountable within the dose range examined (up to 10 mg/kg). Examination of the time course of changes in behavior during the 6-week immunization period revealed a reduction in cocaine, but not food, self-administration during the last 2 weeks of the immunization period in rats with serum antibody levels greater than 0.07 mg/ml. These findings suggest that reductions in drug-seeking behavior and drug intake after immunization with IPC-1010 do not result from a reduced ability of rats to respond on the lever. Furthermore, daily exposure to cocaine during the immunization period does

not influence the ability of the vaccine to produce reductions in cocaine self-administration, which emerge gradually during the immunization period as serum antibody levels rise. These findings also confirm the need for a sufficiently high antibody level to blunt the effects of cocaine over a range of behaviorally reinforcing doses.

### **Brain SPECT Imaging in the assessment and treatment of aggressive behavior: A putative “Reward Deficiency Syndrome (RDS)” behavioral sub-type**

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Brain SPECT imaging is a valuable tool in evaluating patients with violent behavior. SPECT helps to evaluate the functional integrity of those systems frequently implicated in violence, such as the prefrontal cortex, temporal lobes, and anterior cingulate gyrus. Prefrontal cortex problems are often seen with attention and impulse control problems. Temporal lobe problems, especially on the left side, are often involved with violent thoughts and feelings. Anterior cingulate gyrus hyperactivity has been associated with obsessive thinking and cognitive inflexibility. While a number of genetic antecedents have been implicated (serotonergic, catecholaminergic), it is quite interesting that Volkow and associates are reporting, in this conference, that a reduction of Dopamine D2 receptors in addicted subjects was associated with decreased activity in the orbitofrontal cortex and anterior cingulate gyrus. Different kinds of deficits may require different interventions and treatment. For example, prefrontal cortex deficiencies often respond to psychostimulant medication, temporal lobe dysfunction is helped with anticonvulsant medication, and anterior cingulate hyperactivity is often calmed with serotonergic enhancing medications. Therefore, identifying an individual's type of brain dysfunction may have a significant impact on clinical management. SPECT can provide a roadmap for more targeted treatment. Being able to see brain dysfunction also helps patients more readily accept when a problem is present, which invariably improves treatment compliance. Additionally, being able to understand the biological underpinnings of violence and other associated “reward” deficit behaviors will help our society move out of 17<sup>th</sup> Century Dualism toward a more thoughtful approach.

### **Neurofeedback intervention for treatment of attention deficit/hyperactivity disorder**

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ADD/HD is one of the most pervasive and complex disorders of childhood and adolescence. The majority of individuals with this complex continue to experience the majority of their problems in adulthood. ADD/HD is now recognized as having a strong genetic-neurochemical and neurological basis. In our cohort, we found almost 50% of individuals with the hyperactive form have one or more of the abnormal alleles associated with the D2 receptor, transporter or beta hydroxylase genes (Blum, Braverman, Lubar et al. 2000). SPECT, PET, and MRI studies are showing anatomical and metabolic abnormalities in the frontal lobes, especially the anterior cingulate gyrus, prefrontal

cortices, orbitofrontal and medial prefrontal areas and sometimes in the corpus callosum. These deficiencies take on even more meaning when you consider the recent PET research of Volkow's group, showing DA D2 density paucity in these aforementioned brain regions. Behaviorally, ADHD in particular presents a societal tragedy. More than 50% of young males in prison suffer from the hyperactive form of the disorder. Both inattentive and combined form sufferers drop out of school, cannot finish college, lose their jobs and have destroyed marriages. Although there are many evaluative and diagnostic methods for delineating ADD/HD, including continuous performance tests, rating scales and psychometrics, our research, and clinical findings have shown that the quantitative EEG whether from single scalp locations or many can accurately identify nearly 85% of such individuals, up to at least age 30. EEG may be a better predictor than behavioral measures, especially when coupled with gene testing. Our work and that of others represented by more than 60 published papers and many more conference presentations are showing that EEG biofeedback, based on the findings from QEEG can lead to long-term significant improvement in all of the conventional measures that reflect problem areas for this disorder complex. Although stimulants, antidepressants, alpha blockers and many other drugs have been used in the treatment of ADD/HD, which may be a function of one's genome, neurofeedback provides a powerful addition which has been shown to greatly ameliorate the severity and pervasiveness of the disorder.

### **Amino-acid precursor and enkephalinase inhibition therapy: evidence for effectiveness in the treatment of “reward deficiency syndrome(RDS)”, with particular emphasis on eating disorders**

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Earlier work discovered that neurotransmitter restoration via synthesis occurs by oral feeding of certain precursor amino acids to both animals and humans. These amino acid include but are not limited to l-tryptophane, L-5-hydroxytryptophane (*serotonin restoration*), d-phenylalanine (*enkephalin restoration*), l-phenylalanine and l-tyrosine (*dopamine restoration*), l-glutamine (*GABA restoration*). Moreover, work from the laboratory of Blum and associates found evidence for the use of D-phenylalanine in significantly reducing alcohol preference in enkephalin deficient alcohol preferring C57bl mice. Following this work, numerous studies in both animals and humans confirmed the anti-craving properties of not only d-phenylalanine but a combination of the aforementioned amino acids in a number of “reward” behaviors such as alcohol abuse, opiate dependence, cocaine addiction, polysubstance abusers, carbohydrate bingeing among others (Blum; Mathews-Larsen; and Tennant). In a one year follow-up study on DWI offenders, a similar combination caused a prevention of relapse in both alcoholics and cocaine abusers (Brown *et al.* 1990). Moreover, in a two year study of obese subjects, similar neuro-nutrients reduced weight regain, decreased bingeing behavior and eliminated sugar cravings (Blum *et al.* 1997). At Recovery Systems, we have successfully utilized this approach to treat a number of RDS behaviors, especially eating disorders. In a preliminary evaluation, follow-up interviews of six randomly selected former eating disordered female clients (three were also chemically dependent), were

contacted nine months to three years post-treatment to evaluate efficacy of combining targeted nutritional elements (amino-acids, vitamins, digestive enzymes, a diet low in refined carbohydrates, but adequate in calories and other nutrients) with conventional counseling, education, and peer support. Follow-up confirmed significant initial benefits in mood and freedom from compulsive behavior and ideation in 100% tested. While one subject relapsed within six months, the remaining five subjects all sustained, and in some cases exceeded expectations. Following this preliminary evaluation, we evaluated an additional 100 patients and the data collected revealed 98% significant improvement in both mood and reduced substance craving. This work further suggests the positive potential of adding targeted nutritional protocols to conventional treatment elements to improve outcome in an RDS intransigent population. Reference: Julia Ross, *The Diet Cure* (Viking Press, USA 1999; Penguin UK, AU, and USA, 2000).

anxiety ( $19.0 \pm 2.2$ ,  $p < 0.001$ ) while the Placebo group showed no decrease in anxiety ( $2.3 \pm 2.9$ , ns). Among the Active treatment group only 9% made one or more visits to the nurse, while 56% of the Placebo group ( $p < 0.001$  compared to Active) and 48% of the Usual Care group ( $p < 0.002$  compared to Active) made such visits. In summary, these modalities show significant promise for increasing retention of RDS patients in the residential setting and warrants further study.

### **Increasing retention rates among the chemically dependent in residential treatment: auriculotherapy and subluxation-based chiropractic care**

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A randomized study of auriculotherapy versus a capsule placebo group was carried out in a residential setting among 66 residential polysubstance abusing patients (an example of "Reward Deficiency Syndrome [RDS]"). In addition to the traditional points, the Limbic system, Brain, and Zero points were incorporated in the acupuncture group. Using multivariate logistic regression, patients who completed at least 10 days of auriculotherapy and did not receive intercurrent medications were more likely to complete the 30-day residential program than were patients in the comparison group (odds ratio=9.68,  $p=0.026$ ). In addition, a randomized, placebo controlled, single blind study utilizing subluxation-based chiropractic care (Torque Release Technique) was implemented in the same residential setting. Three groups were randomized: active treatment comprising daily adjustments to correct vertebral subluxations using the Integrator adjusting instrument to deliver a set amount of force and direction with an audible click; a placebo treatment utilizing the same instrument but set to deliver zero force with no direction while maintaining the audible click; and a usual care group who followed the general policies of the residential program. The chiropractic and usual care groups each had 33 subjects while the placebo group had 32 subjects. All of the Active group completed the 28-day program, while only 24 (75%) of the placebo group and 19 (56%) of the Usual Care group completed 28 days. These completion rates are significantly different than that for the Active group ( $p < 0.05$ ). A Kaplan-Meier survival analysis showed the probability of retention in the Placebo and Usual Care groups was less than that for the Active treatment group (Log Rank Test,  $p < 0.001$ ). At four weeks the Spielberger State Anxiety scores were  $32.0 \pm 1.6$  for the Active group,  $42.5 \pm 3.0$  for the Placebo group, and  $33.1 \pm 3.7$  for the Usual Care group. The Active and Placebo groups were significantly different at four weeks ( $p < 0.05$ ), with the Active group showing a significant decrease in