

The Pathology of Drugs Abuse in Humans

By: Dr. Desmond Corrigan FPSI, Department of Pharmacognosy, TCD

“There can no longer be any distinction between the so-called soft and hard drugs” declared Professor Gabriel Nahas of Columbia University, New York, when he addressed the opening session of the first International Colloquium on the Physiopathology of Drugs of Abuse in Paris.

His comments were echoed by Jacques Chirac, Mayor of Paris at a reception for the 120 physicians, surgeons, psychiatrists, gynaecologists, paediatricians and pharmaceutical scientists from nine different countries, including Ireland, who attended the meeting jointly sponsored by M. Chirac and a Parisian hospital Pharmacology Department.

The conference was organised by Prof. Nahas who is well known for his books “Marihuana in Science and Medicine” and “Keep off the Grass”. He is also a scientific advisor to EURAD (Europe Against Drugs), a grassroots movement comprised of European parent, youth, and citizen organisations who co-operate in the prevention of drug abuse. EURAD was formally launched at the European Parliament in October 1988 and is partially funded by the EC Commission. Its policy advocates a humane restrictive drug policy of prevention and early intervention to reduce demand for drugs, rather than a total reliance on restricting supplies of drugs.

The meeting was divided into three sessions dealing with Cannabis, Cocaine and Crack and the Opiates respectively, and was designed to give a European audience an update on recent studies of the damaging effects of the three groups of drugs on the human body.

Cannabis and Memory

Dr. Richard Schwartz, a paediatrician from Georgetown University in Washington, reported that, as the perception of the harmfulness of cannabis increased, as a result of education and their own experiences, the use of the drug among High School students has dramatically declined in recent years.

He also noted that the cannabis now on the US market was, at 7% THC, over 600 times more potent than in 1974. This increased strength increased the risks of damage to short-term memory in chronic cannabis users, which has been demonstrated in a number of studies including a recent one conducted by Schwartz. In this study, a group of heavy users (18g of drug/week) were compared with a matched group of non-using adolescents. There was a statistically significant impairment of recent memory in the drug group which was still detectable after a 6 week drug-free interval.

Schwartz’s results tie in with comments made by adult American cannabis users in which 65% reported memory impairment and 45% stated that their ability to concentrate on complex tasks, to think clearly and to get things done, was impaired. It is believed that those with existing learning problems, or with low IQ’s, are more at risk.

Cannabis and Schizophrenia

An investigation of the link between cannabis and schizophrenia in over 50,000 Swedish conscripts was described by Dr. Peter Allebeck of the Karolinska Institute, Stockholm. His aim was to study, over a 14 year period, the relationship between the frequency of reported cannabis use and the development of mental disease. He found that conscripts who smoked cannabis more

than 10 times were 2.3 times more likely to develop schizophrenia compared to those who had never used the drug, while those who had used the drug more than 50 times were 2.9 times more likely to suffer the disease.

Allebeck concluded that it was no longer a question of whether cannabis use could cause schizophrenia but more a question of which type of schizophrenia would develop in which users and in which circumstances.

Cannabis and Cancer

Professor P. Donald, University of California, Sacramento, reported on a group of cannabis smokers who developed squamous cell cancers of the head and neck. 88% of these cancers are usually found, according to Prof. Donald, in 60-64 year olds who are heavy cigarette smokers and/or heavy drinkers. He described a group of 13 people in the 19-35 age group who developed

“One striking feature of this fascinating and informative conference was the fact that the vast bulk of the research into the effects of various drugs of abuse is being carried out in the US, and appallingly little is known about the pattern use and the effects of such drugs many European countries. There are several valid reasons for this: the lack of available resources for one, as well as the significantly higher levels of drug-taking among Americans. However, because a number of European States are toying with legal changes which will increase the availability of these damaging and lethal drugs, it seems foolish, to say the least, for them to do so without taking into account the information presented at this conference and without adequate research into the likely effects of such a change in policy.”

Dr. Corrigan.

cancers of the head, neck, nose and tonsils. On investigation, he discovered that 11 of the group were heavy cannabis users.

While some of the patients he treated engaged in other risky behaviour i.e. heavy tobacco and alcohol use, several others either did not smoke or drink or were light social users of drugs other than cannabis. This report is one of a number of reports of cancer developing in cannabis smokers some 30 years earlier than in other patients. It was not really surprising that the diagnosis of cancers relating to cannabis use should now be on the increase, because it has been known for years that cannabis smoke was more carcinogenic than tobacco.

What was surprising was the frightening information presented in the paper by Prof. Neglia, Minnesota, that 47% of the cases of Acute Non-Lymphoblastic Leukaemia (ANLL) recorded in the US were related to the exposure of the baby in the womb to cannabis smoked by their mothers. This was accidentally discovered during a study originally designed to establish if exposure to solvents, radiation or petroleum products could have caused the leukaemia.

It was found that while contact with these materials by either parent did slightly increase the risk of a child developing ANLL, maternal cannabis use increased the risk 10-fold.

Cannabis and Pregnancy

A major worrying aspect of these findings is that it is known that large numbers of American women use cannabis while they are pregnant. A carefully conducted study at Boston City Hospital, using confidential surveys and urine analysis for drugs of abuse, found, according to paediatrician Dr. S. Parker, that 27% of mothers had used cannabis during pregnancy.

The babies born to these mothers weighed less than those born to non-cannabis users and were significantly shorter in length. These cannabis babies had less muscle mass than normal and were more jittery, more irritable and less attentive. It was found that there was no increase in

major abnormalities, but that in many of the cases, the mother was using alcohol and tobacco in addition to marijuana, resulting in a synergistic effect.

Parker and his colleagues believe that these effects are due to the carbon monoxide in cannabis smoke which reduces the level of oxygen reaching the fetus, and they stress the need to screen the urine of pregnant women for drugs of abuse so that any cannabis users can be advised to stop using the drug.

Cannabis and the Immune System

Professor Friedmann, Florida, lectured on the effects of cannabis and its psychoactive component THC on the immune system. He noted that THC suppressed the *in vitro* proliferation of T-lymphocytes, natural killer cell function and macrophage activity. This he said tied in with reports dating back to 1905 that cannabis users had an enhanced susceptibility to infectious diseases.

In more recent years, there have been reports of cannabis-related enhanced susceptibility to Herpes Simplex Virus, to Legionella and to Listeria. While there is no direct evidence linking cannabis use to a more rapid progression to AIDS in HIV positive individuals, the known ability of THC to suppress a battery of immune system functions strongly suggests that immunocompromised individuals should avoid cannabis.

Cocaine and Crack

The use of imaging techniques to study the effects of both cocaine and cannabis in the brain was described by Dr. Nora Volkow, New York, in two separate presentations. In her account of her recently performed work on cannabis, Dr. Volkow described the technique of PET, or Positron Emission Tomography, which is a non-invasive method of obtaining whole body or specific organ scans using very low doses of short-lived radioisotopes incorporated into normal metabolites, e.g. glucose, or into drug molecules whose binding to specific receptors can be photographed. It is likely that PET, though extremely expensive, will have a major impact on pharmacokinetic studies of many drugs not just drugs of abuse.

In her work on marijuana. Dr. Volkow studied the effect of intoxication on brain metabolism and was surprised to find the highest brain metabolic activity in the cerebellum. It was difficult, she said, to correlate these new findings with the known subjective effects of the cannabis "high" and she postulated the existence of cannabinoid receptors in the cerebellum.

In the cocaine work, she confirmed earlier work which showed a large decrease in cerebral blood flow in chronic cannabis users due to the well-known vasoconstrictive effects of the drug. This undoubtedly explains the high level of strokes in young "crack" (cocaine base which is smoked rather than inhaled or "snorted" intranasally) users. After injections of labelled cocaine, it was clear that the highest uptake of cocaine was in the basal ganglia and that this could be blocked by drugs which bind to noradrenaline uptake receptors. Similar effects were seen in the heart where the binding of the drug in the left ventricle could be blocked by desipramine.

These impressive imaging studies provide confirmation of studies by Nahas and others who have pinpointed the role of Dopamine receptors in many of the harmful effects of cocaine on the brain and cardiovascular system. Arising from these fundamental studies, it is now possible to design pharmacological treatments which can block the effects of cocaine using calcium channel antagonists and ACE inhibitors in combination with diazepam whose function is to improve the permeability of the blood brain barrier to the ACE inhibitors. These treatments have been shown to permit the survival of laboratory animals given normally lethal doses of cocaine.

The fundamental studies also correlated neatly with a presentation on the cardiac complications which result in the deaths of large numbers of young cocaine users in the US. For example, in Maryland, there were 495 deaths in which cocaine was detected at autopsy in a period of 18 months. Many of the victims were aged between 21 and 38 and, in one case, a 21

year old died from severe arteriosclerosis related to cocaine abuse. There was evidence that cocaine use had resulted in a massive release of histamine from mast cells and that arteriosclerotic arteries are more sensitive to the effects of histamine than normal arteries.

Interestingly, morphine also degranulates mast cells in the same way as cocaine, but whether or not this has implications for the cardiovascular health of heroin addicts merits further research.

Cocaine also causes marked aortic arteriosclerosis both in the thoracic and abdominal aortas which can be a cause of cocaine related deaths. A further cause of such deaths is cocaine induced damage to cardiac muscle. There appears to be no justification therefore in attempts to label cocaine as a safe recreational drug when it causes so many deaths in apparently healthy young people due to myocardial infarctions, cardiac spasms, thromboses and necrosis of the myocardium in addition to the strokes already mentioned.

Additional Risks of Cocaine

Those cocaine users who do not die suddenly are, however, still at risk because of the development of dependence, psychoses and depression, all of which are more likely to occur and to be more severe in nature when Crack is involved. This is because of the higher doses and the more rapid onset of action of the drug in the freebase Crack form.

It is difficult to fully appreciate the strength of addiction to cocaine, but the fact that there are measurable physiological responses to external cocaine-related stimuli in addicts, even after several months of abstinence, gives some idea of the tenacity of the dependence. It also highlights the difficulty of preventing relapse in such addicts.

Another risk is of cocaine-induced psychosis which was once rare, but now accounts for two admissions per day in his hospital in Philadelphia, according to Dr. Charles O'Brien. Many cocaine users were extremely depressed and suicide attempts were frequent. Desimipramine was a useful antidepressant in such cases and had the added advantage of reducing the desire of cocaine.

Dr. O'Brien's statistics were supported by Dr. Rosenthal, Medical Director, Phoenix House, which was one of the pioneers of the drug-free therapeutic community approach to drug rehabilitation. Rosenthal reported that 26% of crack users attempted suicide compared to 6% of non-cocaine users, and that women were three times more likely than men to do so. Interestingly, O'Brien also reported that women were the heaviest users of crack and that many engaged in sexual activity with multiple partners while using the drug, thereby increasing the risk of STD's and HIV infections.

Not only were the women themselves at risk but, according to Prof. Finster of Columbia University, many became pregnant and their babies were also at risk due to uterine rupture caused by sudden rises in blood pressure, due to lack of oxygen, premature birth, as well as teratogenic effects on the genitourinary tract, the heart and the ileum. There was now a very high level of drug-related deaths in infants born to cocaine-using mothers, and a high level of abnormalities in babies exposed to cocaine in the womb.

Prof. Finster believed that pregnancy altered the pharmacokinetics of the drug and that there were increased blood levels due to decreased protein binding, thus increasing the risks. In addition to the physical problems, many cocaine babies who survived were developing attention deficit and other behaviour disorders.

Effects of Opiates

The final session of the meeting, devoted to the opiates, was opened by Dr. John Strange a psychiatrist specialising in drug treatment in London, who described the results of brain scans and psychological tests in a unique group of addicts who had been using prescribed pharmaceutical heroin by means of clean injection techniques for more than 20 years. These addicts, originally

from Canada, were aged between 40 and 60 and demonstrated the remarkable tolerance which can build up to opiates, because they were using upwards of 1gm. of pure heroin per day which is some 100 times the normal dose.

Many of the brain scans showed evidence of cortical atrophy and abnormal ventricular brain ratios. The psychometric tests indicated that verbal memory seemed most affected but, overall, there was no consistent pattern of brain impairment, either physical or psychological, in this group which could definitively be attributed to the drug. Strange stated that, based on this fairly unique group, the use of large amounts of pure heroin for many years does not inevitably lead to mental deterioration or death.

It would have been interesting to have had some information about the physical health of the subjects and also data about their ability to function in society.

Opiates and Immunodepression

The chromosome damage and immune depression caused by heroin and other opiates was described by Prof. Faiek from Atlanta. He noted that the percentage of T-Lymphocytes was significantly lower in heroin addicts and that there was an increased risk of cancer in addicts who used heroin either IV, or who smoked pyrolysed heroin or opium.

In one group of addicts, opium users were four times more likely to develop bladder cancer compared to controls, but addicts who also smoked tobacco were a staggering 20 times more likely to have such tumours. High levels of chromosome damage and more chromosome breaks were noted in addicts as were lower percentages of E-rosette forming T cells.

In all, it is clear that opiates can alter immune status through as yet poorly understood interactions with T cell receptors, and may increase the vulnerability of addicts of HIV infection.

Dr. D. Hutchings, who like many of the other speakers is from the University of Columbia, spoke about the effects of heroin and its substitute – methadone – on foetal development. He believed that while methadone maintenance was often used with pregnant addicts, the only real benefit from it was that it was more likely to keep mothers in ante natal care and helped provide a more stable family environment after the child was born. Apart from this, babies born to mother on methadone were more likely to have severe abstinence problems when born, more major infections and to be at increased risk of neurobehavioural problems compared to either babies born to heroin using addicts or to non-addicted mothers.

In children born to addicted parents, was very difficult to determine how much of the behavioural problems were due to the drug exposure and how much to the chaotic lifestyles of the parents.