Meetings

Amphetamine Abuse

The need to understand problems arising from the use of amphetamines in high doses supplied the impetus for a symposium examining ongoing research with amphetamines. Special attention was given to the use of amphetamines in high doses among young adults, who often congregate in what is known as the "speed scene." The symposium was held 5–6 June 1970 at Duke University, Durham, North Carolina.

The information exchange at the meeting indicated that during the past 2 or 3 years a substantial number of research findings have provided new concepts for understanding the nature of amphetamine toxicity. In many respects basic research data correlated well with clinical observations. For example, the gross behavioral alterations presented by the "speed freak" have correlates in laboratory animal models.

Considerable time was spent throughout the symposium discussing the underlying mechanisms related to the specific behaviors associated with amphetamine intoxication. This was best illustrated by the discussions of biochemical and neural substrates of these behaviors. Axel Randrup (Sct. Hans Hospital, Rosklide, Denmark) reviewed the increasing evidence from studies in his own laboratory and elsewhere indicating that amphetamine-induced, stereotyped behavior is produced by an action of amphetamine on dopamine mechanisms in the corpus striatum. The evidence for this conclusion was based on experiments involving the manipulation of catecholamine blockers and their subsequent effect on amphetamine intoxication. Randrup also concluded from his studies that effects on norepinephrine appeared to contribute to the other forms of behavioral excitation (for example, locomotion), while serotoninergic mechanisms are involved in the production of certain postures in birds and head twitches in rats.

Solomon Snyder (Johns Hopkins University School of Medicine) demonstrated that the addition of the β-hydroxyl group to dopamine, producing norepinephrine, confers stereospecificity to norepinephrine in contrast to dopamine. He demonstrated that the *d*-amphetamine has a specifically greater effect on the reuptake of catecholamine from norepinephrine regions of the brain, whereas *l*-amphetamine has about equal potency to *d*-amphetamine in dopamine areas. Experiments from their laboratory have demonstrated that *l*-amphetamine is much more potent in inducing stereotyped behavior than in inducing hyperactivity, which is consistent with the stereospecificity of the norepinephrine receptor site. Saul Schanberg and Jay Cook (Duke University Medical Center) reported that, whereas the usual action of amphetamines blocked norepinephrine reuptake, in rats chronically intoxicated with methamphetamine, reuptake is facilitated 18 to 24 hours after the last injection. Ermino Costa (National Institute of Mental Health) took a strongly antithetical position to that of Randrup and Snyder on the basis of his experiments. He stated that the increase of locomotor activity elicited by *d*-amphetamine was related to an increased turnover rate of dopamine in the brain. Furthermore, stereotyped behavior elicited by *d*-amphetamine is associated neither with accumulation of *p*-hydroxynorephedrine of the brain nor with an increase of turnover rate of striatal dopamine. In fact, he states, if credence is given to his experiments in which *d*-amphetamine was injected after dimethylimipramine, this might suggest that the stereotyped behaviors are associated with an acceleration of the turnover rate of norepinephrine in the brain.

Elaine Sanders-Bush and Fridolin Sulser (Vanderbilt University School of Medicine) introduced the possibility that accumulation of *p*-hydroxynorephedrine is responsible for the tolerance that develops to amphetamine. After comparing the effect of *p*-chloroamphetamine with that of *d*-amphetamine, they concluded that the results of their experiments lent support to the view that the action of *p*-chloramphetamine is mediated through the release of stored catecholamines, whereas storage of norepinephrine appears unnecessary for the central stimulatory action of the amphetamine as long as the synthesis of catecholamines is not impaired.

Bruce Welch and Anna-Marie Welch (Friends of Psychiatric Research, Baltimore, Maryland) described the differential effect of *d*-amphetamines on aggressive mice and on mice that are usually receivers of aggression. The nonaggressors apparently have a much higher survival rate. In addition, mice that live in groups, even those that live in pairs, are more resistant to the lethal effects of the amphetamines than mice that are housed individually. Arnold Mandel (University of California School of Medicine, San Diego) reported on enzyme induction, especially of tyrosine hydroxylase and acetylcholinesterase, as associated with amphetamine intoxication. He speculated that cholinergic compensation is responsible for the behavioral depression after administration of amphetamines in man as well as in experimental animals.

Phillip Bradley (University of Birmingham Medical School, Birmingham, England) described rather elegant experiments in which single units of the reticular area were responsive to both norepinephrine and neurons. Ovidio Durarte-Escalante (Duke University School of Medicine) described the effect of chronic amphetamine intoxication on single neurons as demonstrated by histochemical techniques. Norepinephrine and dopamine were depleted in both nerve terminals and neurons, whereas serotonin and acetylcholinesterase were increased by chronic intoxication with methamphetamine. Neuronal chromatolysis was also evident from sections of various areas to the brainstem. Charles Spooner (University of California School of Medicine, San Diego) noted the action of amphetamines in young chicks. It consisted of a first phase characterized by release and a blockade of norepinephrine uptake by amphetamine, which could be mimicked by systematically administering either norepinephrine or adenosine 3′,5′-monophosphate. He, however, described a longer lasting ex-

citation phase of amphetamine action, at both the behavioral and neuronal discharge levels, that could not be mimicked by the administration of norepinephrine, dopa, 5-hydroxytryptamine, or combinations of these agents. Dopa stimulated the electroencephalographic arousal and increased the multiple unit activity, but it produced none of the postural characteristics of amphetamine excitation.

John Beaton (Alcoholism and Drug Addiction Research Foundation, Toronto, Canada) demonstrated on a basis of Sidman avoidance paradigms that hallucinogenic activity in the amphetamine series is due primarily to an unhindered nitrogen and either an unhindered *para* or *ortho* or a 2,5-methoxy group. He regarded the difference in potency as being related to the energy level of the highest occupied molecular orbit. Robert Pickens (University of Minnesota Health Sciences Center, Minneapolis) reported that characteristics of self-administered amphetamines closely resembled those seen with the analogous stimulant cocaine. There were several features that differentiated self-administration of amphetamines from that of opiates, including the fact that the self-administration was more gradual in onset and intervals between responses were more variable, with no periods of abstinence observed. C. Robert Schuster (University of Chicago) reported that his studies indicated that self-administration of cocaine may be operating through reinforcing mechanisms dependent upon both norepinephrine and acetylcholine; for instance, prior treatment with a drug such as chlorpromazine increased the rate of responding, an indication that chlorpromazine may partially antagonize the reinforcing effect of cocaine. This is in contrast to prior treatment with such drugs as morphine and pentobarbital, which decrease self-administration. Even more specifically, he found that α-methyl-*p*-tyrosine, an inhibitor of norepinephrine synthesis, specifically increases the self-administration rate, indicating that norepinephrine is involved in the reinforcement. Everett Ellinwood (Duke University School of Medicine) reported that rhesus monkeys chronically intoxicated with methamphetamine displayed a much larger repertoire of stereotype behavior than experimental animals lower in the phylogenetic scale did. In general, the forms of these patterns were considerably more analogous to the human patterns than to those of the lower animals tested. The most notable stereotyped patterns were those involving eye-hand probing and examination of movements that could be either directed toward external objects or integrated into grooming responses.

The second day of the symposium was entirely devoted to clinically oriented papers. Jonathan Cole, superintendent, Boston State Hospital, discussed the clinical uses of amphetamines. He summarized his observations by stating that the only unquestionable clinical indications for *d*-amphetamine are hyperkinetic behavior disorders of children and narcolepsy. He felt its value in the treatment of obesity was limited, but effective, if used for short periods in conjunction with dietary restriction. F. Tatetsu (Department of Neuropsychiatry, Kumamoto University, Japan), Burt Angrist (New York University School of Medicine), John Griffith (Vanderbilt University School of Medicine), and Ellinwood all described the psychological aberrations associated with long-term use of high doses of amphetamines. Both Angrist and Griffith stated that a relatively high dose (60 to 300 mg per day) of *d*-amphetamine can produce a rather typical paranoid psychosis, including hallucinations and thinking disorders, in experimental subjects within 1 to 7 days. These studies also indicated that it was not unusual for manic behavior to alternate with the paranoid psychosis.

Ellinwood noted the tendency of psychopathic, schizophrenic, and borderline individuals to develop a psychosis. From observations of stereotyped behavior patterns in both humans and lower animals chronically intoxicated with amphetamines, he concluded that the central nervous system arousal and attention mechanisms were being stimulated and were responsible, in part, for the form of the psychosis. Tatetsu reported that, although most individuals recovered rapidly within a month after withdrawal of amphetamines, other chronic abusers ended in a schizophrenic-like state or in periodic relapses. John Kramer (University of California School of Medicine, Irvine) and Roger Smith and Ricardo Hofer (both of Haight-Ashbury Research Project) gave poignant descriptions of the California "speed" subculture. Kramer described the intravenous use of methamphetamine in high doses, which may lead to euphoria (the "flash"), anorexia, insomnia, paranoia, violence, compulsivity, "over amping," and death. He stated that the probability of complete recovery is great for even the most disorganized high-dose user, if he abstains for 6 to 12 months. This was contrasted both with Angrist's finding that hallucinations may clear early, but thinking disorders may persist, and with Ellinwood's conclusion that, although the major components of the psychosis are in remission after 1 year, delusions may persist even beyond this period.

Hofer suggested that understanding the motives and personality characteristics underlying a transition from the use of psychedelic drugs to amphetamines is important in any consideration of the cultural changes in patterns of drug abuse. After analyzing the phenomenological descriptions his subjects gave of their experiences with amphetamines and psychedelic drugs, Hofer further suggested that those subjects who change to the predominant use of amphetamines do so in response to their increased anxiety and lack of motivation, which is due either to previous use of psychedelic drugs or to personality characteristics that make psychedelic drug use intolerable to the user. Smith discussed the emergence of a unique drug scene, the "speed scene," in which relatively unsophisticated, young, middle-class individuals are caught up in a highly criminalized situation. Lacking appropriate street experiences and "hustling" skills, their frustrated aggression is frequently turned in on themselves or outward to others, leading to the development of a highly unstable, transient, and violent community.

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