CLINICAL PHARMACOLOGICAL STUDY AND EEG CHANGES OF DELTA-9 TETRAHYDRO-CANNABINOL EFFECTS IN HUMAN VOLUNTEERS*

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(1) VIGILANCE CHANGES FOLLOWING THC ADMINISTRATION

(a) *Experimental setting and protocol*

SIX MEMBERS of our psychiatric staff volunteered for the first group-study of Delta 9 THC effects in human subjects. After a 20 min control period of EEG recording prior to drug administration, they received a total 10 mg oral-dose of Delta 9 THC in a sesame-oil vehicle. A second EEG recording session of 90 min was followed by successive 15 min recording sessions every hour and for 5 or 6 hr following THC. Blood sample was collected 3 hr after THC and urine collections 6 and 24 hr later. A light lunch followed the blood sample collection.

A neurological and psychophysiological checking was taken every hour, independently of the EEG's recorded on magnetic tape from five different leads (right and left fronto-parietal, right and left parieto-occipital, bilateral occipital) and further submitted to computer's statistical spectral analysis. One-hour pre-control and post-control EEG recording sessions were conducted under the same conditions, the subjects were lying on a bed with their eyes closed most of the time in a dim-light and sound-attenuated room. Horizontal ocular movements, EKG and respiration were also recorded.

(b) *Mean time-course changes of EEG*

The EEG polygraphic recordings taken over 5 hr following THC administration have been scored according to AGNEW and WEBB (1972) procedures. A distinction was made between slight drowsiness (IA state, with interrupted and diffused alpha rhythm) and sedation (IB state, with low amplitude EEG suppressed alpha and occurring theta rhythm) distinguished from light sleep (II state), moderate and deep sleep (III and IV) and REM-state. Percentages of wakefulness (O-state) and IA, IB, II, III, IV, REM states were computed from each successive hour EEG samples and for each subject. These values were plotted for each subject and averaged between subjects for visual 1 hr sequential analysis of vigilance changes following THC. The mean percentages time-course reveals a dominant arousal state during the first 2 hr and then a sedated state increased towards moderate sleep in the 5th hr following THC.

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(c) *Vigilance changes and individual variability*

In fact, these mean percentages values are not representative of the six subjects, a large variability between subjects being noted. Three subjects presented a tendency towards moderate sleep stages and one of them for instance (Fig. 1) oscillated during the first 4 hr between IA and IB sedated phases, ending with a dominant III state of moderate sleep during the 5th hr after THC. However, the three other subjects were more aroused; one of them presented after the initial arousal a IA state of light drowsiness from the 2nd to the 5th hr after THC (Fig. 2). This last polygraphic

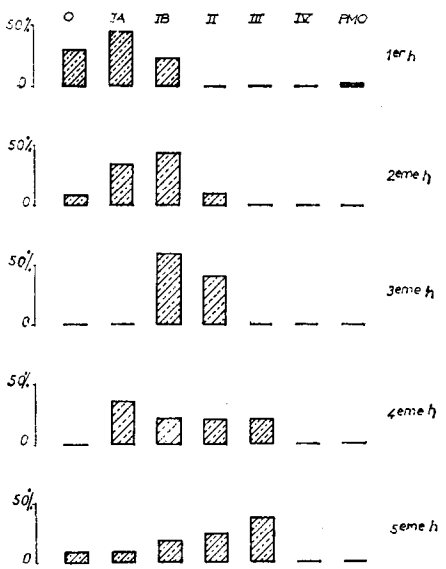

FIG. 1.—One-hour percentage changes of vigilance states following THC administration in one subject presenting a sleep trend through time.

recording presented a time-course hypovariability with an alpha rhythm of high amplitude diffusing over anterior areas. The comparison between the time-courses of 1-hr dominant vigilance phases of each one of the six subjects, indicates a great dispersion between subjects. A trend towards increased deepening of sleep appears at the 5th and 6th hr following THC, which may also be related with the habituation and the monotony of the experimental conditions.

(2) NEUROLOGICAL AND PSYCHOPHYSIOLOGICAL CHANGES

The well-described initial tachychardia (10–20 beats increase in a few minutes), appears when the subject reports the first THC effects, 20–90 min following the oral administration. Some vertiginous sensations have been reported by some subjects during the first 2 hr, whereas conjunctival hyperhemia was observed in all subjects. It appears that the 'eyes-open situation', needed during the clinical and psychophysiological examination is very different from the inner subjective state of consciousness of the 'eyes-closed situation' when the subject is left alone and recorded lying on the bed in order to minimise vertiginous or hypotensive effects of THC. During the

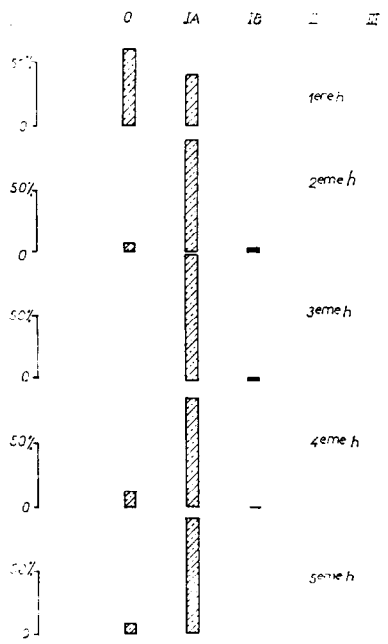

FIG. 2.—One-hour percentage changes of vigilance states following THC administration in another subject presenting of IA-state hypovariability.

successive interviews and clinical testings the subjects have described, after the recording sessions, the intense and vivid visual imagery that occurs in the eyes closed situation. This enhancement of visual scenery was experienced in a moderate euphoric or dysphoric state, depending of the subject, with a more-or-less refusal of answering to the clinical examiner. As many authors have already reported, the subjective reports of our subjects have described difficulties of rational thinking, relaxation and body image changes with oral preoccupations. Three subjects have considered that their total experience provided insight in favour of what can be lived as a primary schizophrenic experience which is in agreement with the model already proposed by JONES (1972).

These dissociated states of 'floating' consciousness, oscillating from hypomanic or oniroïd or confused crepuscular states of vigilance can be related with the observed EEG changes. The problem appears if we have to distinguish or not between these THC-induced subjective dreamy-states and the normal hypnagogic imagery occurring during the on-going of sleep, the REM periods and the hypnopompic imagery sometimes described after awakenings.

(3) VISUAL ANALYSIS OF EEG RECORDINGS FOLLOWING THC

In 4 of our 6 subjects the first 2 hr following THC presented greater arousal time than sedation. Such an arousal recording presents short desynchronised periods which appear similar to hyperaroused phases which occur under an intense mental task or following analeptic treatment.

The peculiar time-course hypervariability of the EEG, following THC administration may be illustrated by the rapid succession of different states of vigilance (Fig. 3). After a deep sedation (IB) followed by some slow-wave sleep patterns (II-III) a mild drowsiness phase occurs (IA) with a high amplitude alpha rhythm specially under

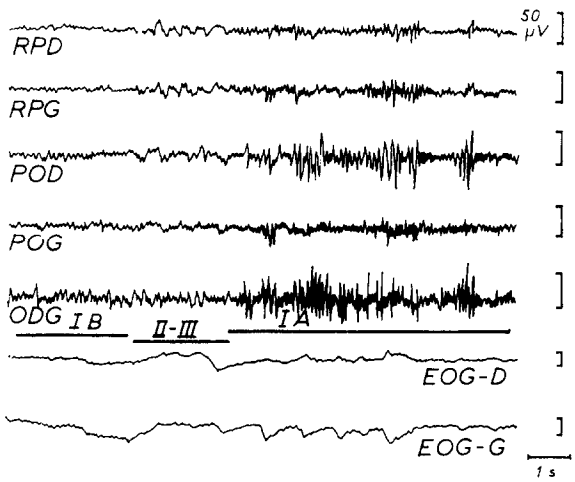

FIG. 3.—Rapid shifts between IB-(II, III)—IA states of vigilance following THC administration in one subject. EEG channels: Right Rolando-Parietal: RPD, left Rol. Par.: RPG, Right Parieto-Occipital: POD, Left Par. Occ.: POG, Occipital Transverse: ODG.

right-left bilateral and right parieto-occipital leads. This time-course variability of vigilance states may to some extent be related to the floating impression and the extreme mobility of the inner subjective impressions and the visual fantasies described by the subjects under THC effects. A REM episode was obtained occurring at the end of an afternoon session, during a control experiment of a subject recorded one month after the THC experiment. The subject being awakened after this recording, was able to describe the content of his dream. This REM episode followed a deep sleep episode and was compared with a recording obtained in the same subject during the THC previous experience and where rapid eye movements occurred between two phases of deep sedation (IB-state). Of course, without chin-muscle recordings or other eye-movements channels, it will be hazardous to assimilate this observed phase of ocular movements with the previous REM episode. However, the Dement and Kleitman hypothesis considering phase I as a 'descending stage one of sleep' and REM as 'emergent stage one of sleep', may be retained at first for those tracings observed in different subjects following THC administration.

In conclusion, from the visual inspection of polygraphic recordings following THC administration, differences in EEG patterns and changes in vigilance time-courses appear, which cannot be wholly explained by considering normal day-sleep recordings more or less facilitated by THC. It is of course difficult to speak of a specific THC-drug induced state, especially when the THC dose is low. The subjective reports have shown an inner visualisation, a highly variable state which appears less inhibited and submitted to the cartesian reasoning and the analytical thinking. A physiological explanation will be founded if a normal functional hemispheric lateralisation was modified following THC administration. Computer's analysis in progress should be able to test this hypothesis. Besides, HEATH (1972–1973) has found EEG changes in deep cerebral structures following THC administration of much greater amplitude than the observed scalp potentials changes and that is another argument in favour of computer's EEG analysis for assessing the slight changes between EEG channels after Delta-9 tetrahydrocannabinol treatment.

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