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Lysergic Acid Diethylamide Effects Modified by Hydroxyzine Hydrochloride *

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"Psychotomimetics", such as Mescaline, LSD 25, LAE 32, Bufotenine, TMA and others, are substances provoking transient psychotoxic reactions in normal persons. In recent years, the problems posed by these drugs have been extensively studied and fully discussed.

As far as the various clinical and interpretative aspects are concerned, the experimental intoxication in man by LSD 25 may be briefly summarized under the followings headings:

(1) Psychopathological, descriptive and structural studies on symptomatology produced in normals (*Stoll; Condrau, Rinkel* et al.; *Abramson* et al., *Anderson* and *Rawnsley, De Shon* et al., *Von Felsinger* et al.), in neurotics and psychotics (*Condrau; Savage; Hoch, Cattel, Pennes; Busch* and *Johnson, Giberti* et al., *Callieri* and *Ravetta, Sanguineti* et al.).

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* Part of this study was communicated at the Soc. It. Biol. Sperimentale, Section of Genova, on July 26, 1956.

(2) Possibilities of the use in psychotherapy (*Frederking*, *Sandison* et al., *Giberti* et al.).

(3) Studies on the effects of some drugs (*Schwartz* et al., *Fabing*, *Giberti* and *Gregoretti*, *Agnew* and *Hoffer*; *Yamada* and *Takuni*, *Ginzel* and *Mayer-Gross*) or other conditions (*Hyde*, *Hubbard*) in order to modify, reduce, prevent or aggravate the psychotoxic syndrome induced by LSD 25 (e. g.: "Model Therapy modifying Model Psychosis", *Osmond* or "Psychopharmacological Antagonism", *Giberti* and *Gregoretti*), with the assumption that compounds useful in the treatment of "artificial" psychosis, may be applied in psychotic subjects.

(4) Biochemical and neurophysiological investigations (*Axelrod* et al., *Hoagland*, *Bain*, *Marazzi*, *Purpura*, *Grundfest*, *Killam* et al.) with the aim of clarifying the mechanism of action of the drug in order to draw clinical and therapeutical implications.

The development of these different points has led to the conception of "model psychosis" (*Fischer*), to the experimentation with drugs with an "antagonistic" action and to some neurophysiological interpretations, indicating that the point of attack of LSD lies in the reticular and mesodiencephalic systems (*Rinaldi* and *Himwich*).

The purposes of this paper are:

(1) Description and hierarchy of symptoms produced by LSD in normals.

(2) Evaluation of any possible action of hydroxyzine hydrochloride in modifying the effects of LSD, when given prior and during the model psychotic experience.

(3) Critical aspects of some interpretative problems concerning the mechanisms of action of LSD on the basis of the neurophysiological literature and partly of personal EEG findings.

Method

The experiments were carried out in five normal males, volunteers (physicians at the Department) in the 28–31 age range.

Following the method adopted in previous work (*Giberti* and *Gregoretti*), the LSD 25 was given orally on an empty stomach in a dose of 100 gammas (1st experiment). In particular, after fifteen or more days from the first intake which constituted the basic control experiment, the subject was submitted to a 2nd dose of LSD (2nd experiment), prior treatment with hydroxyzine hydrochloride * having been given, starting during the 8 hours before the experiment and continuing until a total of 200–225 mg. was reached in the first two or three hours after ingestion of the LSD 25.

* Chlorobenz-hydril-hydroxyethoxy-ethyl-diethilendiammine (commercially Atarax), kindly supplied by the Union Chimique Belge.

The EEG examination was carried out three times during the course of the test, that is at about 1 -4 hours, and from 8 to 10 hours after administration of the LSD 25; control recording of the subject under normal conditions had been made severa days previously.

A third experiment was carried out with LSD and with the administration of a substance without psychotropic activity, with the aim of discovering the existence of any possible emotionally subjective influences.

In all the different experiments the subjects were not aware what possible kinds of effect might be felt from the drugs administered. We purposely did not use a psychometric methodology both because such a technique was partially known to the subjects, and because we were familiar with their psychology.

Results

In the evaluation of the psychotoxic symptomatology provoked by LSD, with and without hydroxyzine hydrochloride, we have considered the following points:

(1) Interval of time between administration of LSD and the appearance of the subjective complaints and symptoms;

(2) Duration of the effects caused by LSD;

(3) Features of the effects caused by LSD;

(4) Modifications induced by hydroxyzine hydrochloride on the model psychotic experience;

(5) EEG findings.

(1) The psychotoxic symptoms appear, after administration of LSD, between 14 and 30 minutes in the 1st experiment and between 30 and 45 minutes in the 2nd experiment with hydroxyzine hydrochloride. Moreover in the 2nd experiment the objective symptoms take place 8–10 minutes later than the subjective complaints.

(2) The psychotoxic effects last between 6 ½ and/or 8 ½ hours in the 1st experiment and between 4 ½ and/or 7 hours in the 2nd experiment. The psychotoxic period was therefore reduced during the simultaneous administration of hydroxyzine, varying from a minimum of 1 ½ hour to a maximum of about 3 ½ hours.

(3) In the first experience the initial complaints concern disturbances of the autonomic nervous system. The subjective feelings of trembling, of muscular weakness, staggering associated with dizziness, heaviness in the joints are the first subjective experience shown by three subjects, while in the other two are subjective sensations of accelerated heart beat, cold and numbness in the mouth.

Objectively the first signs are: restlessness and slight psychomo-

tor excitment (2 cases); euphoria with involuntary laughing, nausea and salivation, apathy and depression (3 cases).

Furthermore, the subsequent psychopathological effects of LSD 25 may be summarized as follows:

a) Perceptual changes: visual distortions of the illusional type; visual hallucinations; gustatory disturbances; hyperacusis;

b) Disturbances of thought: difficulty in concentration and in the power of expression; poverty of thought; impairment of abstract thinking; increased distractibility; acceleration of thought and slowing down of the mental activity, etc.

c) Changes in affect and mood such as feelings of indifference and unreality; depersonalization; anxiety, suspiciousness; depression; euphoria; apathy and behavioural modifications such as restlessness, over/or underactivity, inappropriate smiling or laughing.

d) Autonomic nervous system disturbances: nausea, urgency of micturition; precordial and abdominal discomfort; flushing; changes in pulse rate; etc. Such a symptomatology may be distinguished hierarchically in primary or direct phenomena and secondary or indirect phenomena (see discussion).

(4) The modification induced by hydroxyzine hydrochloride are observed particularly in affect and mood.

In the second experiment (with hydroxyzine hydrochloride) the first complaints concern perception: distortion of visual perception in two cases; paraesthesias in the limbs and sensation of cold in two others; asthenia, discomfortable sense of heart beat in one case. The first objective disturbances are of a vegetative type: nausea, xerostomia, shivering with tremors in three subjects; of emotional type in the two other cases (inhibition and depression in one case and laughter and euphoria in another case).

Unpleasant affective disorders, such as fear, insecurity, suspiciousness, anxiety, depression and restlessness are greatly reduced and weakened. Both from the behaviour and from the words of the subjects, there appears to be a distinctly improved control of the emotional reactions and a considerable reduction in the degree of affective changes usually caused by LSD in the previous experiments. The mood appears to be much more stable; the euphoric behaviour (such as flow of speech, dishinibition, involuntary laughter) disappeared; the subjects seem to be more quiet, and there are greater possibilities in interpersonal relations and in the power of expression.

The intellectual functions, the attentive level, the flow of thoughts, the abstract thinking also appear to be better maintained and more efficient. (For example: even prolonged reading of scientific publications is possible as well as prolonged and difficult conversations, writing, at all hours, and descriptive report of all the experiences was possible, etc.) In the first experiment, in fact, there was an interruption (from three to five hours) in keeping the written report of the subject's experiences, while such an interruption did not occur during the experiment with hydroxyzine hydrochloride.

All subjects also agrree that the second test was less unpleasant than the first.

No significant modifications are noted with regard to the perceptive alterations, hallucinatory phenomena, vegetative symptomatology and depersonalisation. It is our impression that in some subjects the sedative effects of hydroxyzine, by contributing to accentuate a kind of sleepiness, increased the production of a richer and more colourful hallucinatory dream like state.

Mydriasis, flushing of the face, polliakiuria, weakness, as well as strange impressions of taste were maintained almost unchanged. The variations in blood pressure were moderate. Nausea was reduced to a considerable or fair degree, while dryness of the mouth was accentuated in three subjects.

The results of the third control experiment coincided for the most part with those of the first experiment.

(5) All subjects showed in the EEG, during the LSD experience, an increase in the frequency of the alpha rhythm at the rate of 1–3 cycles per second. The administration of hydroxyzine hydrochloride did not change the LSD record; in particular, the increase in frequency noted in the subjects treated with LSD remains unaltered even when the most characteristic and fundamental symptomatology appears to be exhausted.

Discussions

Our observation concerning the LSD syndrome in normal subjects substantially agree with previous data (*Stoll*, *Condrau*, *Rinkel* et al., *Anderson* et al., *Von Felsinger* et al.).

As to the question of nosology and clinical outline of LSD phenomena, it has been assumed by some (*Buscaino*, *De Giacomo*, *Rinkel* et al.) that a remarkable similarity of lysergic symptoms to schizo-

phrenic states is quite undeniable. This point of view is strongly questioned by others (*Blickenstorfer*, *Sarwer-Foner*, *Sanguineti* et al.), who deny to the LSD syndrome any character of clinical entity and consider it so aspecific as any exogenous toxic reaction typically is.

In whatever terms the LSD picture might be described and interpreted, it remains nothing else than an artificial condition, and any comparative speculation with regard to spontaneous psychosis is an exterior analysis. The fact of the matter is that the problem is not only a theoretical, but chiefly a practical one.

In other words what we must debate at the present time is not whether LSD does or does not reproduce a spontaneous psychosis, but whether these experimentally produced psychotic-like states can in some way be utilized in experimental psychiatry.

According to this way of putting the problem, the LSD syndrome can profitably be used, in our opinion, to test drugs which are expected to have therapeutic effects. Of course some caution is needed in the application of these results to spontaneous psychosis. Only general informations are expected from this test and the possibility to use a "model therapy for a model psychosis" *(Osmond)*. We think these concepts were intended by Fischer when speaking of "model psychosis". Obviously this way of using an experimental psychosis implies a precondition: the practical possibility of satisfactorily describing LSD pictures in order to evaluate modifications induced by the drug to be tested. This is an interesting point of our results: by focusing our study on single and limited symptomatological aspects the best possibilities are offered both for psychopathological investigation and for the study of the changes induced by drugs.

In fact, an analysis of the lysergic symptomatology in different subjects and in different psychic syndrome gives sufficiently clear evidence of an arrangement of the psychotoxic phenomenology which, following the views of *Mohr*, *Hoch* et al. and of *Bazzi*, may be indicated as follows: (1) primary symptoms, that is phenomena which are linked to the specific and direct action of the drug and which appear constantly and uniformly (perceptual, thought and neurovegetative disturbances); (2) secondary symptoms which represent the emotional and personality reaction of the individual to the primary action of the drug. Such a symptomatology, which is often characteristic, is linked to the affective structure and to the particular personality disposition of each individual.

In our experience, the purely psychological symptoms (the socalled "magic" effect), that is, the effects produced by suggestion and immagination caused by the representative estimation on the part of the subject, did not appear to us to be either very evident or important.

These are general considerations on which an attempt to testing hydroxyzine hydrochloride has been based. In fact, not only the LSD picture is influenced by hydroxyzine, but an analysis of its effect is to some extent possible: we did not observe a general modification of the LSD syndrome, but the "secondary symptoms" appeared to be selectively modified.

This analytical approach is not frequently met with in the literature, but it deserves a particular emphasis at least for two reasons: firstly, it shows that the distinction previously made between primary and secondary symptoms is not artificial and formal, but a significant one; secondly, it does not support the opinion that the "antagonism" between LSD and other drugs is an antagonism in the strict pharmacological sense, but it suggests that we are dealing with a simple superposition of effects.

The most important changes in the LSD syndrome, due to the effect of other drugs, are above all related to the affect and mood (*Hoch*, *Schwarz* et al.) in the cases of sedative drugs, and only partly and to an uncertain degree (*Agnew* and *Hoffer*), to the affect and mood and to a greater extent to the primary psychotoxic symptoms (*Ginzel* and *Mayer Gross*) for other drugs (for example nicotinic acid and BOL 148).

The "model" therapy, therefore, seems not to act, in many cases, through a competitive interaction or preventive or blocking effect, because this type of action would imply a modification of the whole picture, while in our cases only the secondary symptoms are modified, that is the emotional and personality reactions.

The EEG findings are to be considered apart, because our general knowledge of EEG patterns and correlative psychic conditions does not permit one to draw profitable conclusions as far as this particular problem is concerned.

The problem of the way in which LSD works has been approached by means of electrophysiological experimentation (*Delay* et al., *Rinaldi* and *Himwich*, *King*, *Killiam* et al., *Purpura*, *Marazzi* and *Hart*, *Evarts*, *Buscaino* et al., a. s. o.). Clinical electroencephalography

might also represent a mean of conducting further study, at least within certain limits, of the action of LSD in human beings. The EEG examination during the psychotoxic reaction caused by LSD in our cases has shown an increase in the frequency of the alpha rhythm to the degree of 1–3 cycles per second, in accordance with *Rinkel* et al., *Gastaut* et al. Other authors (*Anderson* and *Rawnsley*, *De Shon* et al., *Sanguinetti* et al.) have found cases with increase of frequency, as well as cases of reduced frequency, and some (*Forrer* and *Goldner*, *Liddel* and *Weil Malherbe*) with an increased responsiveness of the alpha.

At the present time, the chances that the study of electric cerebral activity may bring some clarifying elements to the problem seem to be poor. Recent researches in connection with the problem of relationship between behaviour, state of consciousness and cerebral electrical activity in man (*Gastaut*, *Fischgold* et al. *Loeb* et al.) confirm that it does not seem possible to find valid correlations. Even *Evarts* in a review of the electro-neurophysiological effects of LSD on animals concludes that considerable difficulties exist in finding a relationship between electrical cerebral activity and psychological effects (and in particular emotional disturbances). Our observations that the electric cerebral activity remains unchanged after the intake of LSD, even for many hours, and when subjectively and objectively the subject has retourned to "normal" conditions, still conflicts with the interpretation given by *Gastaut* et al., and shows the difficulties which exist at this time in findings correlation between psychopathological states and electrical cerebral activity.

Summary

Five normal subjects were treated with LSD 25, used as "psychotoxic test" at 100 gammas per os.

The psychopathological effect are described and classified on the basis of their structural hierarchy in primary and secondary phenomena.

During a second experience, hydroxyzine hydrochloride was administered (200–225 mg.) before and during the action of LSD 25.

Hydroxyzine modifies the psychic symptomatology produced by the psychomimetic drug. Such a modification concerns mainly the secundary symptoms i. e. the affect and mood.

The effect of the hydroxyzine, as well as some other drugs, on the

LSD 25 syndrome appears to be not an antagonism in strict pharmacological sense but a simple superposition of effects.

The EEG examination during the psychotoxic reaction caused by LSD 25 shows an increase in the frequency of the alpha rhythm at the rate of 1–3 cps.

Some other aspects of the problem are discussed.

Zusammenfassung

5 normale Personen wurden einem «psychotoxischen Test» unter Verabreichung von LSD 25 (100 gamma per os) unterzogen.

Die psychopathologischen Wirkungen wurden auf Grund ihrer strukturellen Rangordnung in primäre und sekundäre Erscheinungen eingeteilt und dementsprechend beschrieben.

Bei einem zweiten Versuch wurde vor und während der Wirkung des LSD 25 Hydroxyzin Chlorhydrat (200–225 mg) verabreicht.

Das Hydroxyzin verändert die vom psychomimetischen Medikament hervorgerufene psychische Symptomatologie. Die Veränderung betrifft hauptsächlich die sekundären Symptome, d. h. die Gefühle und Stimmungen.

Die Wirkung des Hydroxyzin und anderer Substanzen auf das LSD 25 Syndrom erscheint im streng pharmakologischen Sinne nicht als Antagonismus sondern lediglich als eine Überschneidung von Wirkungen.

Die EEG-Untersuchung während der durch LSD 25 erzeugten psychotoxischen Reaktion zeigt eine Frequenzerhöhung des Alpha-Rhythmus von 1 bis 3 c/s.

Weiterhin sind andere Aspekte des Problems behandelt worden.

Résumé

Cinq sujets normaux reçurent per os 100 gammas de LSD 25, comme «test psychotoxique».

Les effets psychopathologiques en sont décrits et classés sur la base de leur hierarchie structurale, en phénomènes primaires et secondaires. Au cours d'une deuxième expérience, 200 à 225 mg de hydroxyzine hydrochloride furent administrés avant et pendant l'action de LSD 25.

L'hydroxyzine modifie la symptomatologie produite par le produit

psychomimétique. Ces modifications concernent principalement les symptômes secondaires, c'est-à-dire les réactions personnelles psychoréactives survenant dans le cadre des émotions. L'action de l'hydroxyzine sur le syndrome produit par LSD 25, de même que celle d'autres médicaments, semble ne pas être un antagoniste au sens pharmacologique stricte du terme mais plutôt une simple superposition d'actions.

L'examen électroencéphalographique pratiqué au cours de la réaction psychotoxique provoquée par LSD 25 montre une augmentation de la fréquence du rythme alpha de 1 à 3 cycles par seconde.

D'autres aspects du problème sont également discutés.

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