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Relationships Between Chemical Structure and Psychoses with the Use of Psychotoxic Substances

"Comparative Pharmacopsychiatric Analysis:" A New Research Method*

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The study of artificial psychoses involves several problems, namely, the question of psychopathologic characteristics or symptomatology, the somatic basis of these psychoses, the difference between inducing and inhibiting chemical compounds, the eventual specificity of psychotoxic effects, the question of relationship of experimental to schizophrenic psychoses, and the like.

Today it is generally admitted that psychotoxic substances do not provoke specific symptoms whether these substances are of a metabolic or pharmacologic nature. All psychotoxic phenomena can be subsumed under the few "acute exogenous reaction types" of Bonhoeffer. According to this author the other existing symptomatologic differences are largely explained by the psychodynamics of the individual, his personal history, his social milieu, and the experimental situation. Nevertheless there are symptomatologic differences that are not sufficiently explained by these factors and therefore other reasons could be involved.

Recently comparative studies of symptomatic psychoses were performed with three half-synthetic ergot derivatives. These compounds are the well-known lysergic acid diethylamide (LSD) and two others with similar chemical structures. It was shown that the psychotic symptoms produced by these substances, even if chemically similar, gave interesting differences. These differences could not be explained by the psychic constitution of the subject, his life history, his psychodynamics, or the experimental situation.

The question arose, therefore, as to whether there existed an eventual relationship between the chemical structure of the psychotropic compounds on the one hand and certain symptomatologic characteristics produced by them on the other.

In the following study, the psychologic effect of LSD was compared with that of lysergic acid monoethylamide (LAE) and lysergic acid amide (LA). We will not concern ourselves here with the individual content of symptoms but only with their formal appearance, that is, the kind and intensity of alterations in perception, consciousness, thinking, mood, etc.

From structural formulas of the three pharmacologic substances, it can be seen (p. 430) that the side chains in each differ. LSD has two ethyl groups on its amide group, whereas LAE has only one ethyl group and LA is not substituted at all.

It is beyond the scope of this paper to describe the order of experiments on all subjects in detail. Fourteen persons, mainly medical men and chemists, were given LAE and LA

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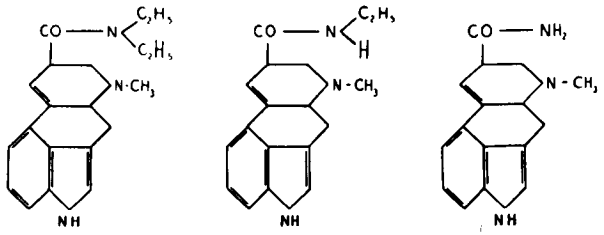

LSD LAE LA

respectively under exactly the same conditions in progressively large doses, and a graded series of 32 psychotic reactions were obtained. It will be shown that the formal aspect of the LAE response is slightly different from that obtained from administration of LA. When LAE was given, the different subjects showed a characteristic psychosis in a rather uniform manner that was striking. With the use of LA, which provokes a slightly different syndrome, the response was also rather uniform. Therefore, and because of considerations of the well-known difficulties of the subjects in repeated experimental psychoses, it was deemed unwarranted to continue administration of LSD on the same persons. The author then compared the results obtained using LAE and LA with the well-analyzed experiments of Stoll and Weyl in which LSD was used. Obviously such a comparison must be done with the greatest prudence, but, since the formal aspects of the responses obtained in the group receiving LSD were also rather uniform, it was deemed somewhat justifiable to compare these data while bearing in mind the aforementioned restrictions. Even then the greatest caution had to be used not to overestimate the results.

1. As is generally well known, the symptomatology of the LSD reaction produced with 25 to 100 gamma given orally or intravenously shows as the most impressive symptom many disturbances in visual perception. (Stoll and Weyl recorded that 56 to 78 per cent with LSD-induced psychoses showed these phenomena.)[1] Much more rare are the perceptual alterations of gustation, audition, and touch. Bodily sensations and changes in body image are seen in almost all subjects. Slight disturbances also occur in thinking as do distortions in the perception of time. Consciousness becomes slightly dreamlike and often leads to certain drowsiness. Self-observation and insight remain intact. Important personality disturbances also occur, namely, feelings of depersonalization and experiences of split personality. There are affective alterations and changes in drive. The subjects often exhibit euphoria, which can change to depression. Furthermore, alterations of the autonomic nervous system appear, especially before the onset of the psychotic phase.

With low doses of LSD the neurovegetative disturbances are paramount; on the other hand, with higher doses hallucinations and the whole psychodynamic personality change predominate. The symptoms begin about one-half hour after administration of the drug and remain intense for a mean of 4 hours. The average total experience lasts 8 hours.

2. The effective dose of LAE is about 10 times as great as that of LSD, showing that it is

more difficult to create optical illusions and hallucinations with LAE than with LSD, even if one considers the big difference between the efficient or working amount of both drugs.

Small doses of LAE produce the same neurovegetative disturbances as do equally small doses of LSD. If LAE is given in a middle range dosage (about 0.5 mg. per injection), it is not the disturbance in visual perception that dominates during the wavelike (up and down) variations in the psychotic symptomatology but rather (in 64 per cent) the phases of extreme abulia, apathy, indifference, and absence of thought (*"Gedankenleere"*) with feelings of changed personality, difficulties of contact with the surroundings but rather normal responsiveness, and slight drowsiness, which is stronger than with use of LSD. Sleep however does not occur. Disturbances in visual perception were seen in only 33 per cent; in principle they corresponded to those of LSD but did not seem so intensive or impressive.

One of the subjects described the lethargic phase as follows: "A state of absolute euphoria, of well-being; everything seems to dissolve in the distance, everything becomes unimportant, there is great indifference and difficulty to think and to remember the past. Will power fades away and doesn't react as usual. . . ." Other subjects perceived this state of being overwhelmed and the inability to resist as disagreeable and pressing.

With increasing doses of LAE (about 0.75 to 1.00 mg. and more per injection) the lethargic-apathetic syndrome occurs more often and more intensively (in 83 per cent). The same pertains to the decrease of consciousness and to the optical hallucinations (in 66.5 per cent). Occasionally the latter symptoms can even dominate the picture for a certain time, so that the same phenomena is obtained as with LSD, particularly hallucinations.

This type of high dosage LAE response, identical to the LSD syndrome, was described by a subject as a succession of "images;" such as many friendly lion heads, birds with white feathers, many men with top hats, spider webs, warriors with trumpets, many pelicans, and many peacock feathers. Everything occurred quickly, changed continuously, and had no connection. At the same time the subject noticed everything that happened around him, especially acoustically. It was as though he existed simultaneously in two worlds, one real and the other a dream. He was fascinated by the experience but was slightly indifferent to reality. The symptoms occurred in succeedingly intensive phases. At the same time a tremor in the masticatory muscles was experienced.

There are, then, no principal differences in the mental symptomatology produced by LSD and LAE. Both drugs can bring about the same symptoms, but in general one can say that LAE produces lethargy, indifference, drowsiness, apathy, and abulia more often than does LSD. The deterioration of consciousness is slightly greater with the use of LAE. Finally, the hallucinatory phenomena, which are exceptional with small doses of LAE, become frequent, intensive, and impressive (as always with LSD) with high amounts of LAE.
3. The effective doses of LA are the same as for LAE, but LA induces greater indifference, a decrease in psychomotor activity, and a desire to sleep much more strongly than does LAE, until finally an increased clouding of consciousness produces sleep. LA may provoke sleep after one-half to one hour; if the subject is not awakened, sleep lasts approximately two hours. If the dose of LA is increased, no certain hallucinatory experiences can be noticed, but uncomfortable autonomic disturbances do occur, such as, hypersalivation, emesis,

dizziness and diarrhea; sometimes irritative depressive moods occur concomitantly. Because of these symptoms the tolerance point was considered reached.

With middle to strong doses in 1 subject work became increasingly difficult after 30 minutes. After forty minutes he began yawning and experienced a sensation of inability to use the limbs, a feeling of sinking into nothing, impaired concentration, and an immediate desire to sleep, after which he slept for three hours during the day.

Using the greatest prudence the following provisory interpretations are proposed. If ethyl groups are substituted on the amide group of LA, its power to produce hallucinations seems to increase. On the contrary, if the number of substituted ethyl groups are decreased, hallucinatory potentials are also weakened; i.e., the visual system seems less affected, but psychomotor activity decreases and clouding of consciousness is augmented until sleep occurs.

Of course it remains unsettled as to whether the observed differences in the psychopathologic and psychotoxic effects of LSD, LAE, and LA depend directly on the structural differences of the side chains of the three drugs. This cannot easily be determined. It is not even known how the psychotropic lysergic acid derivatives become effective in the human organism and where they actually function. One is forced to question whether the psychotoxic substance becomes effective through its total structure, or if the psychosis is caused by a result of its breakdown or through the influence of intermediary metabolites. Another possibility is whether the various psychologic responses to these three compounds depend on the differences in the resorptive, metabolic, and excretory processes of the drugs. Or perhaps a chronologic factor may be involved, that is, one substance may metabolize faster than the other, thereby causing psychopathologic differences. There is also some question as to whether these three drugs attack different hypothetical receptors, such as in the brain. Today we have almost no knowledge about the relationship between chemical structure and psychotic symptomatology of psychotoxic compounds. Why, for example, do the hallucinations dominate in 1 case and a clouding of consciousness dominate in the other? What, for instance, are the somatic conditions for the appearance of hallucinations in symptomatic psychoses?

This paper introduces a new procedure to deal with these questions, which we call *comparative pharmacopsychiatric analysis*. By this is understood pharmacopsychiatric research, wherein one works not only with one specifically defined psychotoxic drug but also with additional compounds that are only slightly modified and therefore remain closely related.

SUMMARY

The psychotic reactions produced by three chemically related lysergic acid derivatives show similarities and differences. Their comparison gives some insight into the problems of the relationships between the chemical structure and the psychotic symptomatology with the use of psychotropic drugs and may facilitate understanding of the somatic foundation of symptomatic psychoses.

Since this research method employs a series of slightly modified psychotoxic substances the name *comparative pharmacopsychiatric analysis* is suggested. This procedure is proposed as a new adjunct for study in experimental psychiatry.

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RESUMEN

La psicosis artificial producida por tres derivados del ácido lisérgico químicamente relacionados, mostró similitudes y diferencias que ayudaron a explicar la relación entre la estructura química y la sintomatología psicótica. Este método de investigación puede constituir una ayuda para mejor entender los fundamentos somáticos de la psicosis sintomática.

RESUME

La comparaison de la symptomatologie des psychoses provoquées par trois dérivés psychotoxiques de l'acide lysergique, apparentés chimiquement, permet de discuter certains rapports entre la structure chimique de la substance psychotrope et l'altération psychotique produite par elle. Et l'auteur propose d'utiliser des substances psychotropes possédant une structure chimique étroitement apparentée pour faciliter l'étude des rapports entre les modifications pathophysiologiques et psychotiques, dans le domaine des psychoses toxiques. Ce nouveau procédé est appelé "analyse pharmacopsychiatrique comparative."

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