NEWS

THE STORY OF LSD 25

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In the last year, more than 90 scientific articles have been written on l-lysergic acid diethylamide (LSD25)*. In turn, the popular press has also taken up this subject, sometimes writing sensational articles where you can read things like LSD 25 causes excessive "madness" in a sane individual, and that the substance can bring an adult to a child's psychological level; or that it provides an extraordinary cure for psychological cases that are generally believed to be almost incurable.

Considering the confusion that certain information, either exaggerated or incorrect, has created; and although this product is of interest primarily to psychiatrists, it is necessary to inform the reader of "TRIANGLE", the development and actual state of research on LSD 25.

1938: ***Chemical synthesis***

After lysergic acid was identified as an essential component of ergot alkaloids[1], it became possible to synthesize a series of semi-synthetic derivatives belonging to this group. Thus, in 1938 A. Stoll and A. Hoffman[2] successfully synthesized, based on lysergic acid, not only ergobasine, a natural alkaloid, but also other derivatives, including *D- lysergic acid diethylamide*. This compound was designated LSD 25 in the laboratory and was subjected to multiple biological analyses that suggest it has a strong uterotonic effect. This effect was not unexpected because of the close relationship with LSD 25 and ergobasine, a notorious oxytocic. We also noted that animals treated with these substances were very excited or cataleptic. Later, these observations were briefly published in March 1943 in the context of a chemistry paper[3,4].

1943: ***Discovery of the Psychic effect in human***

In April 1943, five years after the first synthesis of LSD 25, A. Hoffman was again looking at this substance in the Sandoz research laboratories in Basel. During his work, he felt a strange sensation that he noted in his laboratory notebook as follows.

> "Friday, April 16, in the afternoon, I was forced to stop my work and go home to seek relief because I was taken by an undesirable agitation accompanied by light dizziness. Once at home, I lay down and fell into a state of semi-inebriety, slightly agreeable, and characterized by extreme activity of the imagination. Closing my eyes (daylight was very disagreeable to me) I saw, like in a kaleidoscope, a stream of uninterrupted and fantastic images with extraordinary relief and richness of color. This state continued for about two hours."

Hoffman deduced that there was probably a relationship between the curious phenomenon that he was victim of and the substance he manipulated earlier in the lab – D-lysergic diethyl amide - although he didn't take it intentionally, and only a trace

* Registered trademark: Délyside

amount could have fortuitously penetrated his body. To be certain, he decided on a self-experiment. To be prudent, he ingested 0.25 mg of LSD 25, which seemed a small quantity compared to doses used for other ergot derivatives. The experience soon demonstrated that 0.25mg represented five to ten times the dose required to induce psychiatric-like disorders in most normal persons. This explained the intensity of the reaction that Hoffman experienced. About 40 minutes after he ingested the drug, he noted the first symptoms: "slight dizziness, agitation, difficulty to concentrate, visual trouble, excess hilarity".

> "This is where the annotation stopped in my lab notebook. It was with extreme difficulty that I succeeded to write the last word. I asked my lab assistant to accompany me to my home, thinking that things would evolve as the previous Friday. But I realized on the way, on my bicycle, that my reaction was more intense than the last time. I felt great difficulty in expressing myself clearly; my vision field oscillated and appeared distorted, as if images reflected from a deformed mirror. I also had the impression that I was not moving forward but my assistant later affirmed to me that we were actually moving quite fast."
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> "To the best of my memory, while experiencing the maximum effect of the drug, and even before the medical doctor arrived, I felt the following symptoms: dizziness, visual disturbances, faces of people surrounding me appeared as grimacing, colored masks; alternating symptoms of motor agitation and paralysis; my head, my limbs and my whole body felt very heavy, as if they were full of lead. Cramps in the calf, my hands were occasionally cold and sensitive; metallic taste on my tongue, throat was dry and contracted; shortness of breath; phases of unconsciousness; and then I was back into a normal state; sometime I saw things as if I were an outside and impartial observer, that I was screaming like a demented man, or that I was gibbering in a disorganized manner.

The doctor found a weak pulse but no other circulatory symptoms. Six hours after ingesting the drug,

> "My state was for the most part normalized. Only visual disturbances were still strong. Everything seems to oscillate and deform, like an image reflected by agitated, rippling water. Everything was bathed in changing, disagreeable colors that were dominated mainly by venomous green and blue tones. When I close my eyes, I was constantly assailed by images that were colored, fantastic and extremely plastic. A curious phenomenon was that the acoustic perception, (for example the noise of a car on the street), were transposed into optic sensations; the slightest sound, the slightest noise, induced colored images with changing form and hues – resembling the figures of a kaleidoscope."

After a night of deep sleep, Hoffman woke up "in perfect health, although slightly tired." After this adventure, no doubt remained about the extreme effect of LSD 25 and in particular, its effect on psychic function in humans. Other collaborators of Sandoz laboratories repeated the assay on themselves and confirmed Hoffman's observations.

These first experiments were published by A.W. Stoll in 1947[5] in a systematic study of the substance carried out at the University of Zurich Psychiatric Clinic. Henceforth, this work established a complete description of the intense intoxication provoked by LSD 25 in both normal and schizophrenic subjects, in such a way that only minor details have since completed the picture.

Symptomology of the intense intoxication by LSD 25

The ingestion by mouth of a very small quantity of LSD 25, on the order of ½ to 2 μg (0.0005 to 0.002mg) per kilogram of body weight provoked, after a latent period of about half an hour to 2 hours, psychic alteration that can last from five to twenty-four hours or sometimes longer.

At the beginning, we also noted certain somatic and neuro-vegetative symptoms: slight motor uncoordination, pupillary dilation, tachycardia, nausea, and occasional hyperhidrosis, and hypersalivation, etc. However, these physical manifestations are not as strong as some of the alterations in visual disturbances, thought and affect.

All in all, there are no obvious changes in consciousness or memory. On the other hand, time appreciation is often distorted, sometimes time passes either too fast or too slowly than in reality. Certain mental processes are accelerated while others are reduced. There are diminutions of attention and capacity to concentrate.

Affectivity can be modified in one way or another: euphoria, exuberance, excessive hilarity, or on the contrary, depression, anguish. There is often an alternating face of euphoria and depression.

Form and colors frequently appeared altered. Properly speaking, the hallucinations, either optic or auditory, are not rare when you are in the dark or with eyes closed.

On some occasions, the subject feels a very curious sense of depersonalization or split personality. For instance, the subject has the sentiment to observe himself from the exterior; to float above the body; or to have completely lost contact with normal reality. He often has the impression that he's grown or, on the contrary, decreases in size. This illusion is often limited to certain body parts; in some cases, there's the impression that these parts become dissociated from the body.

Concomitant with the illusion of becoming smaller, the subject often regresses back to his childhood, to a point where he re-experiences childhood events with great accuracy.

Figures 1-9 give an idea of some of the effects produced by one dose of LSD 25 given to a painter. MÁTÉFI[6] volunteered himself to repeat, hour after hour, the portrait of the same model before and after the action of 100ug LSD 25 observed by os. This series of drawings illustrates in perfect accuracy, the increased motor uncoordination, the progressive changes in visual perception, and an expanding humor expressed as rapid

strokes (Figs 5-7). And finally, the gradual diminution of symptoms and gradual return back to a normal state (Figures 8 & 9).

The inebriated or dream-like state produced by LSD 25 can be grouped among the intense psychoses induced by consumption of exogenous intoxicants. Its symptomology reminds us in part of the manic depressive psychoses with psychomotor excitation, euphoria or depression. In particular, it reminds us of schizophrenia with hallucination and depersonalization.

These psychic alterations attenuate progressively over a few hours. In particular, they are completely disappeared the morning after the ingestion.

The etiologic problem of psychoses

Well before the discovery of LSD 25, we were aware that certain substances can cause psychic and mental aberrations. Alcohol inebriation is also characterized by symptoms that reflect a primary cerebral dysfunction. Other drugs such as cocaine, opiates, hashish, mescaline and amphetamines are equally producers of hallucinations. In summary, what makes LSD 25 unique is not '*what it produces'* but *how it acts*. LSD distinguishes itself from all of the other drugs in this category by the fact that it is active at extremely small doses. This observation is very important for medical sciences and in particular, for psychiatry. Although the causes of mental diseases remain unknown for the most part, we often ask ourselves whether defective metabolism might produce certain toxic byproducts that could alter the delicate functioning of cells of the nervous system.

LSD 25 is obviously not a substance made by the body but its mode of action is closely related to some hypothetical endogenous substance. We therefore have at our disposal, thanks to LSD, a compound that will allow us to undertake, under a new light, studies of nervous system that are the bases of mental and intellectual processes.

We probably have a better understanding of the pathogenesis and the mechanism of psychosis once we have elucidated the biological phenomena that precede the psychic reaction that are induced by D-lysergic acid diethylamide. This problem is under intense investigation by multiple researchers[7-11].

We have recently discovered[12,13] that LSD 25 is the most powerful known antagonist of 5-hydroxytryptamine (serotonin, enteramine)(Figure 10). This effect deserves mention because serotonin is naturally produced in our body, is shown to be in the brain and that it might play an important role in the mechanism of cerebral function[14]. *

Self-experiments with LSD 25

Thanks to LSD 25, it is possible to transiently induce a psychic state that is closely related to schizophrenia or manic depression without compromising the integrity of the

* The reader will find in the next edition of 'Triangle' a detailed study of the properties and biological function of serotonin (5-hydroxytryptamine or enteramine).

body. This property offers psychiatrists the possibility, which is precious to more than one group, to try the substance on themselves, and thus enter, for a few hours, the psychic world of people with mental diseases. Numerous authors[6,15-19] have tried the experience and their conclusions are instructive.

Therapeutic Possibilities

In neurotic people, LSD intoxication is likely to cause the recall of ancient events from childhood that are either forgotten or suppressed and it can also help them to understand the origins of their emotional trauma. Therefore, in the appropriate situation, this product can facilitate psychotherapy treatment[20-23].

So far, LSD 25 has proven itself to be useful mainly in the treatment of anxiety and obsessive compulsive disorders that normally require extremely long psychotherapy. With weekly treatment with LSD 25, we have succeeded in some cases to improve the psychic state in a few weeks or months. It is obvious that LSD treatment can only be done either in a clinical setting or under strict supervision of a psychiatrist. Extreme prudence is required for subjects who show propensity to develop psychoses.

In truth, the therapeutic usage of this interesting substance is in its infancy and it would be premature for us to pronounce the range of its applications at this moment.

Figure Legends

Figure 1: Charcoal drawing done 20 minutes after the ingestion of 50 µg of LSD 25. State is still normal. 40 minutes after the drawing, the subject took another 50 µg of LSD.

Figure 2: Rough charcoal sketch, 1 hour 25 minutes after the ingestion of the first dose and 25 minutes after the second dose of LSD. Euphoric state. The experimental subject (M.) sees the model correctly but is having difficulty reproducing the exact proportions. The hand holding the charcoal is making poorly controlled movements with excessive amplitude.

Figure 3: Charcoal drawing 2 hours and 30 minutes after the first ingestion of LSD 25. M. sees normally the profile of his model but with exaggerated relief and modified colors. He painfully tried hard to make a good drawing but unsuccessfully: "my hand must follow the line of movement. I have the impression that my awareness is fixed in the part of my body that is functioning."

Figure 4: Sketch done a few minutes after drawing in number 3. "The contour of the model is normal, those of my drawings are not (fig. 3). I pulled myself together and tried again: it is not working! On the third try, I surrendered (fig. 4).

Figure 5: Sketch done shortly after drawings 3 and 4. "I restarted and produced this drawing in one trace."

Figure 6: Drawing in color (tempera), 2 hours and 45 minutes after the first dose of LSD. M. is agitated. "The perspective of the piece is changed. Everything is in movement…everything is ordered in a colored network…the model's face is transformed into a diabolical mask."

Figure 7: Colored drawing (quill and watercolor) 4 hours 25 minutes after the first dose of LSD. Euphoric state; signs of inebriety are slightly diminished. M. tried to reproduce a portrait resembling the first drawing and remarked; "at the slightest inattention, the movement of my hand escaped."

Figure 8: Sketch in color (pencil), 5 hours 45 minutes after the first dose of LSD. "It is probably because of my uncoordinated gestures that I can no longer draw as usual…I feel and see myself somewhat bathing in a stream of cascading euphoria. Now, it is down to my knees; soon enough, only a spiraling current will remain."

Figure 9: Charcoal drawing, 8 hours after the first dose of LSD. The intoxication has almost entirely disappeared except for a few escaping waves: for instance in the space of

a few seconds, faces transiently appear deformed. M. feels distracted and tired. "I have nothing to say about this last drawing; it is bad and boring."

Figure 10: Dog posterior hind leg perfusion. Measurements of femoral artery pressure. At the start, 30 µg of serotonin (S_1) and 1 µg of adrenaline (A) produced the same vasoconstrictor effect. After adding LSD 25 to the venous circulatory pool, (final concentration = 1:1 million), serotonin doses of 30 µg (S_1), 100 µg (S_2) and 250 µg (S_3) no longer have any effect while the action of 1µg of adrenaline is only slightly reduced (based on GINZEL and KOTTEGODA[13]).

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