

## The Mode of Action of Taraxein and LSD

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Taraxein is the name adopted by Heath, et al.<sup>1,2,3</sup> for a principle of schizophrenic serum, capable of inducing a psychotic-like state in monkeys and in human volunteers with alterations in the depth EEG—especially in the hippocampus and septal region—similar to alterations found in schizophrenics. This report deals with the interaction of taraxein isolated according to Heath, et al.,<sup>1</sup> and of LSD with different psychotropic drugs i.a. acetylcholine, adrenaline, adrenolutin, atropine, mescaline, serotonin and a phenothiazine.

We have been able to confirm that intravenous administration to Rhesus monkeys of an amount of taraxein, isolated from 400 ml. of schizophrenic serum, produces within 15 minutes a withdrawal pattern including catatonic features which lasts for at least half an hour. Stimulation of the animals increases the withdrawal. The phenomenon often appears in waves, interchanged with more normal behavior. Kabi 888 given intravenously to monkeys and cats at the dose level of 10-12.5 mg., corresponding to 2-3 mg./kg. causes no observable clinical changes. Heath<sup>1</sup> in confirmatory preliminary trials found no changes in the subcortical and cortical EEG recordings.

Apart from the experiments in which we administered taraxein alone to Rhesus monkeys, different batches of taraxein were given prior to Kabi 888. Control experiments were performed with deteriorated taraxein and with the corresponding fraction isolated from normal serum. All experiments with active taraxein gave the same clear-cut results. At the height of the taraxein effect as described above, 10 mg. of Kabi 888, corresponding to 2-3 mg./kg., were injected intravenously. There was immediate loss of muscle tone, general pilo-erection, and a deep sleep which was clinically separable from the taraxein reaction (Figure 1). These symptoms lasted for 10 to 15 minutes, followed by a return to the taraxein behavior.

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Deteriorated taraxein and the corresponding fraction from normal serum did not produce the typical taraxein effect. Kabi 888 given after inactive taraxein did not cause any changes like those noted when given after the injection of active taraxein. Utilizing monkeys with subcortical electrodes Heath<sup>1</sup> has confirmed our observations and found that Kabi 888 given intravenously subsequent to taraxein exerted a profound central activity starting in the hippocampus and the septal region.

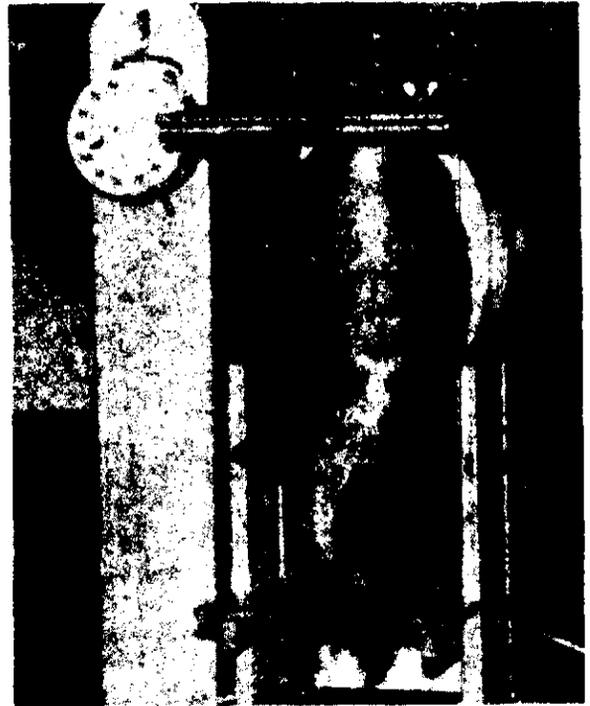


Figure 1

In order to investigate whether similarities existed between taraxein and LSD the above described experiments were repeated with LSD instead of taraxein. The same monkeys which received Kabi 888 in conjunction with taraxein were used. LSD was given intravenously in an amount of 50-100 microg., corresponding to 15-30 microg./kg. Within 15 minutes a slight withdrawal was noticeable and the monkeys became slightly catatonic.

At this stage 2-3 mg./kg. of Kabi 888

were given intravenously, immediately resulting in a complete loss of muscle tone, followed by a sleep-like state lasting for about 10 minutes. Half an hour later the Kabi 888 dose was repeated with the same striking effect. Heath<sup>1</sup> confirmed that premedication with LSD seems to enhance the central nervous system effects from Kabi 888. To judge from the EEG readings there appears, however, to be a qualitative difference in addition to a quantitative difference between taraxein plus Kabi 888 and LSD plus Kabi 888.

Hoffer<sup>6</sup> and Osmond<sup>7</sup> have carried out volunteer trials utilizing adrenolutin as a psychotomimetic agent. In our studies adrenolutin exerted only a slight pharmacodynamic activity when given intravenously to monkeys or cats in the dose range of 20-25 mg./kg. After premedication with taraxein or LSD, however, even as little as 2-3 mg./kg. of adrenolutin intravenously produced drowsiness and muscular relaxation. Heath<sup>1</sup> gave higher doses of our adrenolutin producing a stuporous state. Experiments in cats premedicated with 15-20 microg./kg. of LSD intravenously, followed by 2-3 mg./kg. intravenously of Kabi 888 or adrenolutin gave the same result as described above in monkeys. Hoffer<sup>6</sup> applying our technique to humans has confirmed our findings that premedication with low doses of LSD enhances the activity of adrenolutin given later.

Feldberg and Sherwood<sup>9</sup> and Schwarz, et al.,<sup>10</sup> have reported on the striking behavioral changes in cats after intraventricular administration of i.a. acetylcholine, adrenaline, adrenolutin, atropine, mescaline and serotonin. Using these drugs we carried out experiments in cats, serving as their own controls. The dose range chosen, 0.1-1 mg./kg. intravenously, produced none or only negligible clinical changes in the control experiments. After premedication with LSD the same amount of the drugs administered intravenously caused the same striking central effects.

Preliminary studies with acetyl-LSD (ALD) and bromo-LSD (BOL) given in the same dose range as LSD indicate that the

above properties of LSD are found in ALD but not in BOL.<sup>2</sup>

Cerletti<sup>11</sup> summing up the pharmacodynamic properties of LSD suggests that the psychotomimetic part of the LSD effect might involve a "trigger function." Heath, et al.,<sup>12</sup> after a series of experiments in monkeys with taraxein followed by Kabi 888 and adrenolutin according to our technique discuss various possibilities of the mode of action of taraxein e.g. interference with amine metabolism or permeability changes of the blood-brain-barrier. Our experiments discussed above suggest that taraxein and LSD both have the property of enabling certain intravenously injected drugs to act on selected brain centers, not normally accessible to them. Endogenous compounds present in the blood might also produce behavioral changes through the same mechanism.

*Authors' Note:* LSD, ALD and BOL were kindly supplied by Dr. A. Cerletti of Sandoz, Basle, Switzerland.

#### REFERENCES

1. Heath, R. G., Mårtens, S., Leach, B. E., Cohen, M., and Angel, C.: *Am. J. Psychiat.*, 114, 14.
2. Heath, R. G., Mårtens, S., Leach, B. E., Cohen, M., and Feigley, C. A.: "Behavioral Changes in Nonpsychotic Volunteers Following the Administration of Taraxein, the Substance Obtained from Serum of Schizophrenic Patients." *113th Annual Meeting of the American Psychiatric Association*, Chicago, May 13-17, 1957.
3. Heath, R. G., Leach, B. E., Mårtens, S., and Cohen, M.: "Studies in Mid-Brain Relationships, Behavioral Changes with Administration of Taraxein, a Substance Extracted from Schizophrenic Serum." *113th Annual Meeting of the American Psychiatric Association*, Chicago, May 13-17.
4. Heath, R. G.: Personal communication.
5. Hoffer, A.: *J. Clin. Exptl. Psychopath. & Quart. Rev. Psychiat. Neurol.*, 18, 27 (1957).
6. Hoffer, A.: *Hormones, Brain Function and Behavior*. Academic Press, Inc., Publishers, New York, 1957, p. 181.
7. Osmond, H.: *Ann. N. Y. Acad. Sci.*, 66: 418.
8. Hoffer, A.: Personal communication.
9. Feldberg, W., and Sherwood, S. L.: *J. Physiol.*, 123: 148 (1954).
10. Schwarz, B. E., Wakim, K. G., Bickford, R. G., and Lichtenheld, F. R.: *Arch. Neurol. Psychiat.*, 75, 83 (1956).
11. Cerletti, A.: "Die Pharmakologie des LSD mit besonderer Berücksichtigung der Beziehungen zum Serotonin." Stockholm, October 14, 1957.
12. Heath, R. G., Leach, B. E., and Cohen, M.: To be published.