Princeton, N. J. New York: Josiah Macy, Jr. Foundation, 1956.
17. Osmond, H., and Smythies, J.: Schizophrenia: A new approach, I. *J. Ment. Sc., 98:* 309–315, 1952.
18. Hoffer, A., Osmond, H., and Smythies, J.: Schizophrenia: A new approach, II. Result of a year's research. *J. Ment. Sc., 100:* 29–45, 1954.
19. Personal communication.
20. Personal communication.
21. Heirman, P.: L'adrénoxine, adrénaline oxydée inhibitrice. *Comptes rendus Soc. de Biologie,* Paris, *126:* 1264, 1937.
22. Heirman, P.: Quelques propriétés physiques de l'adrénoxine. *Comptes rendus Soc. de Biologie,* Paris, *127:* 345, 1938.
23. Heirman, P., and Goffart, M.: Action mydriatique de l'adrénoxine. *Comptes rendus Soc. de Biologie,* Paris, *132:* 84, 1939.
24. Page, I. H.: Serotonin (5-hydroxytryptamine). *Physiol. Rev., 34:* 563–588, 1954.
25. Gaddum, J. H.: Antagonism between lysergic acid diethylamide and 5-hydroxytryptamine. *J. Physiol., 121:* 15P, 1953.
26. Woolley, D. W., and Shaw, E.: Some neurophysiological aspects of serotonin. *Brit. M. J., 2:* 122, 1954.
27. Woolley, D. W., and Shaw, E.: A biochemical and pharmacological suggestion about certain mental disorders. *Proc. Nat. Acad. Sc., USA, 40:* 228, 1954.
28. Woolley, D. W., and Shaw, E. N.: Evidence for the participation of serotonin in mental processes. *Science, 124:* 34, 1956.
29. Cerletti, A., and Rothlin, E.: Role of 5-hydroxytryptamine in mental diseases and its antagonism to lysergic acid derivatives. *Nature, 176:* 785, 1955.
30. Marrazzi, A. S.: Nerve impulse transmission and related problems. Proceedings, Council for High Blood Pressure Research, American Heart Association, 1954, pp. 6–37.
31. Marrazzi, A. S.: Ganglionic and central transmission. *Pharmacol. Rev., 6:* 105–106, 1954.
32. Frederking, W.: Ueber die Verwendung von Rauschdrogen (Meskalin und Lysergsäure-diaethylamid) in der Psychotherapie. *Psyche, 6:* 342, 1953/54.
33. Frederking, W.: Intoxicant drugs (mescaline and lysergic acid diethylamide) in psychotherapy. *J. Nerv. & Ment. Dis., 121:* 262–266, 1955.
34. Sandison, R. A., Spencer, A. M., and Whitelaw, J. D. A.: The therapeutic value of lysergic acid diethylamide in mental illness. *J. Ment. Sc., 100:* 491–507, 1954.
35. Denber, H. C. B., and Merlis, S.: A note on some therapeutic implications of the mescaline-induced state. *Psychiatric. Quart., 28:* 635–640, 1954.
36. Denber, H. C. B., and Merlis, S.: Studies on mescaline. I. Action in schizophrenic patients. *Psychiatric. Quart., 29:* 421–429, 1955.
37. Denber, H. C. B.: Studies on mescaline. III. Action in epileptics. *Psychiatric. Quart., 29:* 433–438, 1955.
38. Denber, H. C. B., and Merlis, S.: Studies on mescaline. VI. Therapeutic aspects of the mescaline-chlorpromazine combination. *J. Nerv. & Ment. Dis., 122:* 463–469, 1955.
39. Denber, H. C. B.: Studies on mescaline. VII. The role of anxiety in the mescaline-induced state and its effect upon the therapeutic result. *J. Nerv. & Ment. Dis.* (In press).
40. Abramson, H. A.: Lysergic acid diethylamide (LSD-25). III. As an adjunct to psychotherapy with elimination of fear of homosexuality. *J. Psychol., 39:* 127, 1955.

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BIOLOGICAL CHANGES IN MAN FOLLOWING INTRAVENOUS ADMINISTRATION OF MESCALINE

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This report concerns a research investigation carried out under the supervision of Professor Jean Delay, in collaboration with Drs. M. Raclot, J. Thuillier, and M. Ropert. Its main purpose was to study the biological reactions to intravenous mescaline, of which little is known. Renewal of interest during the last few years in the hallucinogens, or "psychosomimetic" compounds, has been concerned particularly with the psychological aspects. Mescaline and LSD have been used experimentally to create psychopathological states comparable to some psychotic disturbances. The ability of various substances to reverse these states has confirmed, in addition, the therapeutic effectiveness of chlorpromazine. "Psychosomimetic" compounds have been used therapeutically as an aid in accelerating psychoanalytic therapy.

It was felt useful to determine if mescaline, besides its specific psychodynamic properties, could bring about any biological reactions similar to those described in connection with shock or stress reactions. This would be of importance in the interpretation of various therapeutic results.

Heffter (1), who isolated the drug in 1894, initiated biological research with mescaline.

The most interesting recent studies have been those related to the search for mescaline antagonists. Quastel and Wheatley (2) in their work on the "cerveau isole" and Schueler (3) with *in vivo* studies demonstrated the action of sodium succinate. This has been confirmed by Delay *et al.* (4). Hoch (5) reported that the combination of amytal-methedrine gave excellent results in blocking the mescaline-induced state. The amphetamines apparently act on the perceptual disturbances. Some barbiturates, such as sodium amytal or pentothal, seem to have a sedative action on the mescaline-induced state.

The neuroleptics have been among the more recent mescaline antagonists studied. Clinical studies and electroencephalographic observations by various authors (5–8) have confirmed that chlorpromazine can counteract the mescaline intoxication with its attendant autonomic disturbances. Reserpine (5) acts in the same way but more weakly. Frenquel has a similar property according to Rinaldi and Himwich (9).

We have been able to demonstrate experimentally (10) that chlorpromazine can block the action of mescaline. The rise in blood pressure brought about by the intravenous injection of mescaline in the rabbit is prevented by premedication with chlorpromazine.

Method

Thirty-seven patients were studied while hospitalized at the University Psychiatric Clinic (Clinique St. Anne) in Paris. Mescaline hydrochloride was injected intravenously (10 mg. of mescaline base per kilo of body weight) at the rate of 2 cc. per minute. The patient was fasting, lying in bed, in a quiet room. Only the physician was present. Various tests were performed routinely immediately before the injection, ten minutes afterwards, at one-half hour, one hour, two hours and four hours. The different measurements of autonomic nervous system reactivity were made at the same time and then every three hours until the twenty-fourth hour. The experimental mescaline state was either allowed to follow its normal course towards complete resolution within 24 hours, or was interrupted by the intramuscular injection of 50 mg. of chlorpromazine one or two hours after the injection of mescaline. Finally, we were able to record electroencephalograms in 10 patients while under the effects of mescaline. Polygraphic recordings were made in some cases. Twenty-five of 37 patients were systematically studied following the intravenous administration of mescaline.

Results

1. *Neurovegetative symptoms*

These are the first signs of mescaline intoxication; a fact already noted heretofore. Nausea with or without vomiting may appear immediately following the injection. In most cases it stops within the first hour. With some patients nausea continues but disappears after the administration of chlorpromazine. The patients begin to perspire almost immediately. Mydriasis develops fairly quickly, either in the course of the injection or within 10 minutes, and lasts about 24 hours. The vasomotor phenomena occur very early. An unusually intense but temporary congestion of the face appears during the injection, decreases progressively, and disappears during the first half-hour. It is replaced by a more or less intensely pale facies. A symmetrical acrocyanosis of the upper and lower extremities is noted during the first 10 minutes, and lasts from one to several hours. Finally, a generalized tremor appears by the second hour. It is often severe, partially under voluntary control. It stops spontaneously after several hours, but is abolished by the injection of chlorpromazine.

Pulse and blood pressure gave rather uniform data with the various subjects and even with one individual after repeated trials. The pulse rate increased in all patients, sometimes as soon as the injection was completed. It progressively increased most often during the first half-hour. The average increase was 28 beats per minute. The pulse rate remained stationary until the fourth or fifth hour after the injection, and then decreased to its initial level after the twenty-fourth hour. In 21 of 25 patients, mescaline increased the systolic and diastolic blood pressure from one to five centimeters of mercury. The blood pressure began to increase within 20 minutes following the injection, reached a maximum within the first hour and often remained at this level until the fourth hour. It then decreased progressively

until the twenty-fourth hour, and returned to the initial or slightly lower levels.

The temperature showed rather consistent variations. Hypothermia was generally observed during the first hours, with a fall as low as 97.2°F. There was a rapid shift at the fourth hour in the direction of moderate hyperthermia, reaching and sometimes going above 100.4°F.

The respiratory amplitude and frequency increased leading to an intense polypnea. The amplitude was always increased, at least during the first hour. The frequency increased from three to five respiratory movements per minute during the first hour, and usually returned to basal levels after the second hour.

As soon as the pulse accelerated, the oculocardiac reflex could no longer be elicited.

2. *Chemical determinations*

(a) The *blood sugar* (table 1) showed a rather consistent elevation during the first 10 minutes after the intravenous injection of mescaline. It reached a maximum after 30 to 60 minutes had elapsed and returned to the initial level between two and four hours. The blood sugar increased 33 mg. per cent (average of 19 patients). Since the averge initial blood sugar was 94 mg. per cent, this would correspond to a change of 35.1 per cent from the average initial value.

TABLE I.—Blood Sugar—(mg. %)

Patients	Before Mescaline Inj.	After Mescaline			
		10 min.	30 min.	1 hour	2 hours
MON	0.80	1.10	1.25	1.25	1.25
RAT	0.92	1.13	1.34	1.34	1.34
MAL	1.06	1.13	1.20	1.20	1.15
BAC	0.90	1.06	1.06	1.10	0.84
CHA	1.00	1.10	1.25	1.25	1.05
SZE	0.93	0.93	1.15	0.93	1.01
PRO	0.94	1.04	1.27	1.70	1.77
LEC	0.97	0.97	0.97	1.06	1.06
RIG	1.01	1.10	1.19	1.01	1.01
RUG	1.06	1.17	1.20	1.48	1.20
MIS	1.01	1.10	1.27	1.16	1.10
NAK	0.95	1.19	1.27	1.22	1.01
WUL	1.01	1.27	1.48	1.34	1.18
HER	1.06	1.34	1.19	1.19	1.01
ARN	0.92	1.04	1.31	1.17	1.02
HOM	0.82	1.02	1.16	1.16	0.94
FER	1.01	1.13	1.13	1.34	1.34
JEG	0.94	0.94	1.16	1.16	1.10
NED	0.84	1.06	1.17	1.17	0.99

The first three patients received 50 mg. of intramuscular chlorpromazine after the 60-minute blood sample was taken.

TABLE 2.—Blood Potassium—(meq./liter)

Patients	Before Mescaline Inj.	After mescaline			
		10 min.	30 min.	1 hour	2 hours
MON	0.195	0.181	0.162	0.162	0.150
RAT	0.180	0.168	0.163	0.150	0.158
MAL	0.204	0.204	0.192	0.192	0.170
BAC	0.168	0.156	0.144	0.150	0.160
CHA	Hemolyzed	0.130	0.120	0.120	0.140
SZE	0.192	0.180	0.192	0.198	0.192
PRO	0.180	0.168	0.150	0.146	0.156
LEC	0.192	0.184	0.184	0.171	0.177
RIG	0.210	0.190	0.180	0.190	0.194
RIG	0.204	0.189	0.186	0.180	0.186
RUG	0.186	0.180	0.168	0.168	0.174
MIS	0.204	0.196	0.174	0.170	0.189
NAK	0.196	0.186	0.180	0.189	—
WUL	0.198	0.180	0.174	0.174	0.174
RIB	0.192	0.172	0.168	0.168	0.180
HER	0.192	0.180	—	0.186	0.186
ARN	0.192	0.180	0.172	0.172	0.172
HOM	0.186	0.174	0.162	0.162	—
FER	0.198	0.180	0.178	0.174	0.180
JEG	0.192	0.192	0.186	0.180	0.162
NED	0.190	—	0.168	0.168	0.178

The first three patients received 50 mg. of intramuscular chlorpromazine after the 60-minute blood samples were drawn.

(b) *Blood potassium* (table 2). There was a consistent decrease within the first 10 minutes after the injection of mescaline. The potassium reached its lowest point between 30 and 60 minutes afterwards and had not returned to the initial levels by the second hour. The average decrease of potassium (milliequivalents) was 0.51 meq. per liter. The initial average value was 4.93 meq. per liter. This corresponded to a change of 12.3 per cent.

(c) The determination of sodium and chloride (intracellular and plasma), as well as proteins, did not disclose any appreciable variations during our experimental investigations.

(d) *Urine* (table 3). An increased urinary excretion of the total 17-ketosteroids, averaging 4.7 mg., was found in 10 of 16 patients during the 24-hour post-mescaline period. The initial average value was 11.1 mg., and the

average change was 42.3 per cent. Excretion during the 24 hours was decreased by an average of 2.7 mg. in six cases.

TABLE 3.—CHANGES IN 24-HOUR URINARY 17-KETOSTEROID EXCRETION (MG.)

Patients	Before Mescaline	After Mescaline
MON	25.8	25.0
RAT	6.1	18.4
MAL	9.0	10.6
BAC	14.5	12.7
SZE	12.0	15.0
PRO	13.0	18.4
ABA	4.2	19.2
BRA	11.5	4.2
LEC	17.8	20.2
MIS	6.8	7.0
NAK	10.3	8.8
ARN	10.0	5.2
GAU	13.4	16.0
NED	5.5	10.0
HRA	8.7	9.3
HAV	10.3	10.2

TABLE 4.—CHANGES IN LEUKOCYTE COUNT

Patients	Before Mescaline Inj.	After Mescaline				
		10 min.	30 min.	1 hour	2 hours	4 hours
MON	9,400	18,400	—	12,000	9,000	—
RAT	9,400	9,100	9,500	13,800	19,700	—
MAL	11,000	17,000	13,900	10,700	22,100	
BAC	6,700	8,900	Coagulated	12,100	—	18,700
CHA	10,300	11,800	16,400	11,900	17,500	20,200
SZE	8,700	10,900	9,900	12,900	12,700	16,600
PRO	15,600	22,700	18,000	17,600	26,400	24,200
LEC	5,800	5,400	6,100	7,000	15,200	9,100
RUG	7,400	15,000	14,900	14,800	14,800	18,100
RIB	7,800	10,000	10,800	11,500	14,800	14,800
HRA	6,300	6,900	7,100	6,300	6,800	6,500
NED	4,400	—	—	4,600	—	13,500
HER	8,000	—	—	8,400	—	15,000
JEG	7,600	—	—	8,400	—	13,600
HOM	8,700	—	—	10,000	—	12,400
GAU	5,500	—	—	6,500	—	14,900
MAL (2nd test)	11,700	—	—	12,900	—	15,700
HOM (2nd test)	8,900	—	—	8,800	—	11,400
HAV	6,900	—	—	12,800	—	19,200

The first three patients received 50 mg. of intramuscular chlorpromazine after the 60-minute blood samples were drawn.

TABLE 5.—EOSINOPHILE COUNT

Patients	Before Mescaline Inj.	After Mescaline				
		10 min.	30 min.	1 hour	2 hours	4 hours
MON	271	243	—	219	136	—
RAT	151	135	162	156	44	
MAL	156	141	117	126	36	—
BAC	109	107	—	92		18
CHA	256	253	160	155	33	7
SZE	94	62	61	45	30	5
PRO	518	532	659	557	252	18
LEC	108	106	82	45	26	7
RUG	140	206	195	203	56	15
RIB	163	180	157	132	47	3
HRA	39	31	27	31	38	35
NED	124	—	—	74	—	3
HER	112	—	—	67	—	5
JEG	60	—	—	29	—	3
HOM	167	—	—	155	—	6
GAU	252	—	—	122	—	6
MAL (2nd test)	111	—	—	31	38	35
HOM (2nd test)	125	—	—	128	—	6
HAV	174	—	—	122	—	8

The first three patients received 50 mg. of intramuscular chlorpromazine after the 60-minute blood samples were drawn.

3. *Hematologic changes* (table 4)

All patients showed a marked leukocytosis reaching its highest level between the second and fourth hours. This was followed by a slow decline to basal levels at the twenty-fourth hour. The initial average value was 8,400. The average increase was 8,000. This represented a 95 per cent change from the initial levels.

Eosinophile count (table 5). The sharp eosinophile fall (Thorn test) was most marked at the fourth hour, and still present at 24 hours. The initial average value was 164. The average fall was 155 eosinophiles. This was equivalent to a change of 94.3 per cent from the initial levels.

4. *Electroencephalographic observations*

G. Verdeaux (1950) found that with oral mescaline the alpha rhythm was blocked at the moment hallucinations occurred. This is a fairly common phenomenon and is probably due to the attention set.

Electroencephalographic observations were

made on 10 patients in this study following the intravenous injection of mescaline. The wave forms were fairly flat; probably the result of a persistent blocking effect. This could have resulted from a more intense reaction due to the intravenous mescaline. The flattened record with disappearance of alpha activity made impossible any correlation with psychosensory phenomena.

5. *Polygraphic studies*

Three patients with an excellent alpha per cent time were studied with the polygraph. This test was run with the patient at rest, listening to music, or being questioned. In spite of fairly strong reactions, there were no real changes of the psychogalvanic reflex. Cardiac and respiratory rhythms were usually normal. Comparison of variations in the psychogalvanic reflex with those of alpha activity was found not to be significant. The polygraphic studies showed the emotional reactions to be insignificant in spite of alpha blocking.

Discussion

Our data may be interpreted in various ways. It would seem that some of the autonomic symptoms are characteristic of mescaline itself. These are the early and persistent mydriasis, immediate and generalized sweating, acrocyanosis, nausea and vomiting. The latter are very rarely absent. Symptoms like polypnea and tremor are difficult to interpret. It is probable that they result from a specific action of the drug and are accentuated by the psychological state of the patient.

Finally, the constant modification of pulse, arterial blood pressure and temperature may be linked to the organic stress reactions. This concept can be substantiated by the unequivocal and significant modification of body fluids in some patients (hyperglycemia, fall in blood potassium, leukocytosis with eosinopenia). These variations were always in the same direction and usually significant. The interpretation of data on the excretion of 17-ketosteroids is difficult. The technical problems inherent in these determinations are well known, and obtaining 24-hour urine specimens in a psychiatric service is most difficult.

Conclusions

1. Some biological constants that we have studied are consistently modified in the same direction. Many of these changes were characteristic of the mescaline-induced state.

2. There was a constant increase in blood sugar, a persistent fall in blood potassium, a marked leukocytosis with an equally abrupt fall of the eosinophiles. The increase in 17-ketosteroids was inconstant.

3. These results seem to suggest a general bodily response to external stress. In this particular case, we suggest use of the term "mescaline shock". This concept would have to be considered in evaluating the various therapeutic results that have been reported.

4. In studying the mechanism of the mescaline stress reactions it is not possible at this time to differentiate the latter from the psychological stress precipitated by the intravenously injected drug.

BIBLIOGRAPHY

1. Heffter, A.: Uber Peotle. *Arch. exper. Path. u. Pharmacol., 34:* 2975, 1894.
2. Quastel, J. H., and Wheatley, A. H. M.: The effects of amines on oxidations of the brain. *Biochem. J., 27:* 1609–1613, 1933.
3. Schueler, F. W.: Effect of succinate in mescaline hallucinations. *J. Lab. & Clin. Med., 33:* 1297–1303, 1948.
4. Delay, J., Gerard, H. P., et Thuillier, J.: Toxicité aigue du sulfate de mescaline et antidotisme du succinate de sodium. *Comptes rendus Soc. de Biologie, Paris, 144:* 163, 1950.
5. Hoch, P. H.: Experimental psychiatry. *Am. J. Psychiat., 111:* 787–790, 1955.
6. Denber, H. C. B.: Chlorpromazine and Mescaline: Colloque international sur la chlorpromazine et les médicaments neuroleptiques en clinique psychiatrique. Paris, 20–22, Octobre, 1955. Encéphale (In press).
7. Denber, H. C. B., and Merlis, S.: A note on some therapeutic implications of the mescaline-induced state. *Psychiatric. Quart., 28:* 635–640, 1954.
8. Schwartz, B. E., Bickford, R. G., and Rome, H. P.: Reversibility of induced psychosis with chlorpromazine. *Proc. Staff Meet. Mayo Clin., 30:* 407–417, 1955.
9. Rinaldi, F., and Himwich, H. E.: The cerebral electroencephalographic changes induced by LSD and mescaline are corrected by Frenquel. *J. Nerv. & Ment. Dis., 122:* 929–932, 1955.
10. Delay, J., Demner, P., Ropert, M., and Thuillier, J.: Antagonisme de la mescaline et de la chlorpromazine. *Comptes rendus Soc. de Biologie, Paris* (In press).

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