Medicine. — *Experimental catatonia by means of derivatives of mescaline and adrenaline.* By L. NOTEBOOM. From the neurophysiological laboratory (Dr. H. DE JONG) of the neurological clinic of the University of Amsterdam (Professor Dr. B. BROUWER). (Communicated by Prof. B. BROUWER).

(Communicated at the meeting of September 29, 1934).

The idea of experimental catatonia, formed by DE JONG and BARUK [1]), consists of the following phenomena, which may be considered as an analogue of the syndrome of the human catatonia:

a) At a lower dosage:

1. Catalepsy; i.e. the active retaining of passively given postures.
2. Negativism: passive or active resistance against change of already assumed attitudes.
3. Autonomic phenomena: Polypnoea, salivation, etc.

b) At a higher dosage:

Hyperkinesia and abnormal postures.

Later it became apparent to DE JONG [2]) that also mescaline and a great number of other substances in part of their field of action may cause catatonic phenomena. In this connection he arrived at the formulation that experimental catatonia is a frequently occurring reaction of the central nervous system.

The question which gave occasion to this investigation was whether there is a connection between the chemical formulas of the various substances which exhibit this catatonic action, in other words whether there would exist a chemical "catatonizing nucleus".

The substances of which it has been proved that they produce such a catatonic action are numerous; of most of them, however, a very accurate dosage is necessary in order to obtain a sufficient effect. Only with bulbocapnine and mescaline it is possible, with fairly different doses, yet clearly, to demonstrate the various phenomena.

Mescaline, a strongly acting catatonicum [3]) of simple chemical composition, has been the starting-point for the greater part of this investigation.

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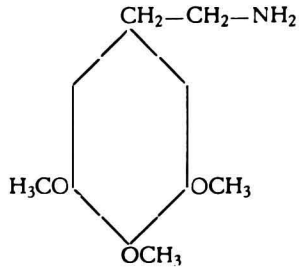
[1]) H. DE JONG and H. BARUK: "La catatonie expérimentale par la bulbocapnine". Masson 1930.

[2]) H. DE JONG: "Die experimentelle Katatonie als vielfach vorkommende Reaktionsform des Zentralnervensystems". Zeitschr. f. d. ges. Neur. u. Psych. 1932, Bd. **139**, ¾ Heft, bl. 468.

Annales médico-psychologiques. N⁰. 2, Février, 1933, N⁰. 2.

[3]) ————: Ueber Meskalin-Katatonie, etc. Proceedings Kon. Akad. v. Wetensch Amsterdam. Vol. XXXIII N⁰. 9, 1930.

First several derivatives of mescaline were examined, which at the centre as well as at the side chain were varied.



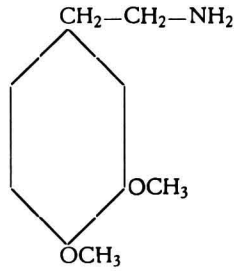
Mescaline. 3, 4, 5-trimethoxy-phenyl-aethyl-amine.

The firm HOFFMAN LAROCHE, of Basel, has been so kind as to compound the substances for our laboratory disinterestedly, for which we here wish to express our great indebtedness.

The substances in the form of hydrochloric salts were readily soluble in water; they were subcutaneously injected in cats in progressive doses.

We now give a summary of the results which varieties of mescaline.

I. *Substance* 1949.



3, 4-dimethoxy-phenyl-aethyl-amine.

This substance clearly appeared to give the syndrome of experimental catatonia in cats, as appears from some typical instances of the many protocols.

The investigation was made on tame, fairly quiet cats of the female sex, as it had appeared that wildness and restlessness of the animals disturbed the experiments and retarded the effect of the catatonizing substances. Loud noises and changes into bright light hindered the experiments as well and made it much harder to judge. Even with strongly acting substances comparatively small matters can form a considerable impediment in finding the correct dosage. For these experiments the cat is particularly suited, as one is mostly well acquainted with her nature and movements and she does not, as the rabbit, sometimes by touching get into a cataleptoid state (so-called "hypnotic catalepsy"). Some orientating experiments were also carried out on mice.

The following may serve as an example of one of the protocols:

Cat B. Weight 2.7 Kg. Tame and lively animal, is easily injected.
11.45 Injection of 150 mg of substance 1949.

12.10 Salivation, vomiting, lack of motility. Wide pupils, slightly responding to light. Shyness and tendency to hide, which makes the impression that the animal is afraid.

12.15 Stands for a moment in the same posture.

12.20 Still in the same posture, the head is moved in a normal manner, reacts also affectively ; stands for about a quarter of an hour in unusual, difficult postures, which she has been given.

Conclusion : Catalepsy, negativism and some autonomic phenomena in doses of 40 to 60 mg of the substance to every Kg of the cat. Hyperkinesiae were seen in the cat only in a short stage just before the fatal dose. Consequently in this experimental animal the hypokinetic phenomena of catatonia can be shown most distinctly.

By means of some experiments on mice, however, it appeared clearly that the complete syndrome of catatonia may be obtained by varying the dose.

A. Moderate dose :

Mouse, 18 gr. Motility normal. August 4, 1931.

11 o'clock Injection of ½ cc (2.5 mg).

11.10 Placed on the Bunsen burner, she goes down and stops, the forelegs resting on the transverse projection, the head downward, and the hind legs upward against the burner ; remains in this posture for a considerable time.

B. Gradually progressing dose :

Mouse, 19 gr. August 3, 1931.

11 o'clock Injection of ½ cc (2.5 mg).

11.10 Mouse is placed on the Bunsen burner, goes down, sits perfectly still for a considerable time with the forelegs on the transverse projection, the hind legs up, and the head down.

11.20 Distinct catalepsy.

11.25 2nd injection of ½ cc.

11.30 marked catalepsy.

11.35 3rd injection of ½ cc : still strongly cataleptic ; also shows active and passive negativism.

11.45 4th injection of ½ cc : when placed on the Bunsen burner, she remains there, sitting perfectly still.

11.50 At the 5th injection of the same dose the animal sits on the table without moving ; she cannot very well hold on to the Bunsen burner any longer.

11.55 Another injection of the same dose makes the animal stand actively on her legs on the table ; she still shows a marked negativism.

12.00 Injection of ½ cc. The mouse, when placed at the foot of the Bunsen burner, tries to climb up, falls down, gets some convulsions, and sits still on the table.

12.05 The mouse makes some "mechanical" walking movements; if the animal is put on her side, walking movements occur, followed by some convulsions.

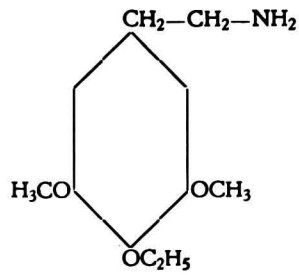
Conclusion: Catalepsy, negativism, not strongly pronounced hyperkinesiae, then convulsions, so complete catatonia.

Another protocol is given here, from which it appears that at a small increase above the medium dose an intermediary stage occurs, just as with bulbocapnine, which influences the motility little to not at all. If the dose is still more increased, paralyses and convulsions occur. The following protocol gives an example of the dosage of 200 mg to a cat of 2.5 Kg.

4.00 Injection of 200 mg of substance 1949.
4.10 Motility normal.
4.15 Retarded movements. The cat looks round and swings her tail. If pushed, she slightly resists change of posture (negativism), responds normally to stroking by rubbing her head against one (sensorium retained).
4.20 No salivation, moves still spontaneously but slowly; her look becomes staring. Begins spontaneously to walk backwards.
4.25 Vomiting. Motility retarded.
4.30 Climbs up against the bars, tendency to stretch, stands for a moment in the posture in which she has been placed; reaction to sounds and motility almost normal.
4.40 Resists change of attitude (negativism), stands unsteadily on her legs, walks spontaneously.
4.50 Remains in the same posture, movements unsteady.

The final conclusion of substance 1949 in the cat (at a medium dose) is that catalepsy, negativism and autonomic phenomena may be aroused by it, while at the same time abnormal postures are assumed and reactions occur, suggestive of fear. If the dose is increased, paralyses, convulsions and death occur, sometimes via an intermediary stage of normal motility. In the mouse also some grosser hyperkinesiae were perceptible at the larger dosage. Putting everything together, *substance 1949 is consequently able to produce the complete phenomena of experimental catatonia.*

II. *Substance* 1950.



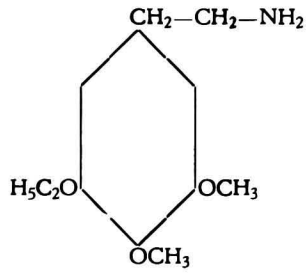
3, 5-dimethoxy-, 4-aethoxyphenyl-aethylamine.

Then there is experimented with substance 1950. This substance also clearly gave toxic phenomena, in which the catatonic element comes less strongly to the front. Phenomena of fear on the other hand dominate.

Gray cat. N⁰. 4. Weight 3,5 Kg. Tame, quiet, easily injected. The injection is not painful.

4.05 Injection of 100 mg of substance 1950.
4.10 extremely fearful, motility normal.
4.20 fearful, motility normal.
4.30 walks and jumps in a normal way.
4.40 has her mouth open, still walks well. Stands with crooked back, wide pupils. Walks back, suddenly turns to different sides, runs off without cause. Dyspnoea.
5.00 Dyspnoea, hangs on the bars for a long time, jumps on the floor, walks very well, then makes unwarranted leaps and movements, all at once runs off. Moves spontaneously on the floor with small steps, crooked back and her tail between her legs.
5.10 Fearful, steals on the floor with crooked back, dyspnoea. If put on a ladder, she remains for some time in the posture in which she has been placed, responds to her surroundings with fear, bites straw, objects to being taken up, and continuously walks spontaneously with small steps, crooked back and hairs on end.
5.30 Still walks spontaneously slowly on the floor. Can walk and jump well.

III. *Substance* 1951.



3, 4-Dimethoxy-, 5-aethoxyphenyl-aethylamine.

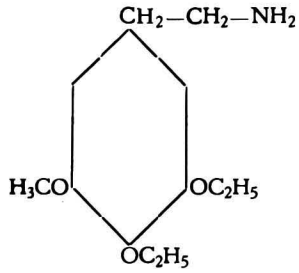
A somewhat analogous picture to that of substance 1950 was presented by substance 1951.

White cat with dark spots. Weight 3.4 Kg. Tame and quiet, easily injected.

3.25 Injection 90 mg of substance 1951.
3.35 Rather shy, motility normal.
3.45 Motility normal.
4.00 She hesitates before jumping, sits slightly shrunk up. Somewhat retarded motility, does not object to being taken up, does not hang on the bars.

4.15 Stands for about 5 minutes on the hind legs in the posture in which she has been placed, walks slowly, reacts to sounds and touch, looks round. All the time the body remains in the same posture.
4.30 Still slow, still remains standing upright. Her look is staring. Walks a little more quickly again, jumps well, sits in a corner.
4.45 Becomes more lively again, still sits slightly shrunk up, walks and jumps well, still hangs on the bars a little longer than normal.

IV. *Substance* 1952.



3, 4-diaethoxy-, 5-methoxyphenyl-aethylamine.

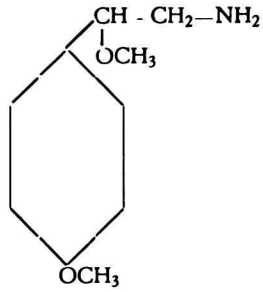
Substance 1952 produced the following phenomena :

It appeared to be a strongly toxic substance, as may be seen in the following protocol.

Black cat with white snout. Weight 3.75 Kg. Quiet cat, offers resistance when injected. Injection not painful.
3.40 Injection of 200 mg of substance 1952.
3.45 Looks round fearfully, sits shrunk up, slow in her movements, hangs on the bars, creeps slowly down and jumps on the floor, reacts little to touch. Stands for a long time upright, does not offer resistance.
4.00 Can no longer walk well, passes urine. Flaccid.
4.30 Lies on the floor, weak, reacts little, does not move spontaneously, and cannot walk.

The next day not yet able to walk, 2 days afterwards dead.

V. *Substance* 1953.



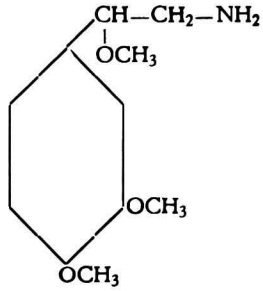
p-methoxyphenyl-, β-methoxyaethyl-amine.

Black cat with white breast. Weight 4.6 Kg. Quiet, tame cat, easily injected. Injection not painful.

3.20 Injection 220 mg of substance 1953.
4.35 Sits still, responds strongly to sounds, then looks round fearfully, retarded in the spontaneous movements. Walks and jumps well.
5.00 Retarded ; stands for a moment on the hind legs, as she has been placed ; walks and jumps well.
5.15 Tendency to stand in the same posture, walks and jumps well, wide pupils. Motility practically normal.

The next day well again.

VI. *Substance* 1954.

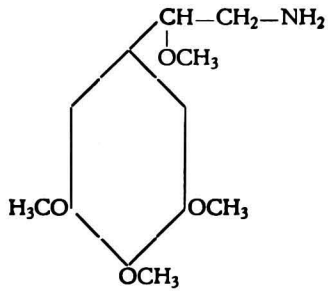


3, 4-dimethoxyphenyl-, β-methoxyaethyl-amine

Gray cat. Weight 2.7 Kg. Tame and quiet. Easily injected. Injection not painful.

3.30 Injection of 100 mg of substance 1954.
3.45 Motility retarded, suddenly spits at flies, then lies quietly in a corner.
4.00 Pronounced retardation. Jumps normally, does not hang on the bars.
4.15 Stands in the posture in which she has been placed. Jumps from the bars on the floor. Looks round, responds to the surroundings.
4.30 Still slow, but more lively.

VII. *Substance* 1955.



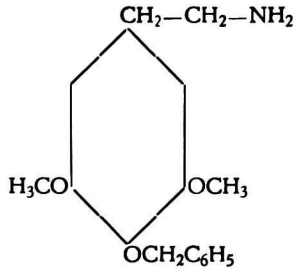
3, 4, 5-trimethoxyphenyl-, β-methoxy-aethyl-amine.

Gray cat. Weight 3.25 Kg. Tame and lively. Easily injected, injection not painful.

3.25 Injection of 200 mg of substance 1955.

3.35 Motility normal.
3.45 The same.
4.00 Spits, if approached ; is slow in her movements. Stands for a long time against the bars of the cage, if she is put up against them. Mews and moves her head. Responds little to sounds and touch. Very little to sounds. Allows herself to be stroked and mews, but retains the same posture.
4.30 Is still standing in the same attitude. Then for about 5 minutes she hangs on the bars with her 4 paws. At last she jumps on the floor, stands in an uncomfortable posture with crooked back. Walks slowly and stiffly. Reacts little to touch, suddenly begins to spit.
4.45 Still stands on her hind legs against the bars, sometimes snatches in the air with a foreleg. Looks round, a moment afterwards again staring fixedly at one point. Spits without reason.
5.00 Has been standing on her hind legs all this time, objects to change of posture (negativism), keeps her tail in the posture in which it has been placed. If thrown down, she always comes down again on her four feet. Stands in unusual posture.
5.15 Takes spontaneously a few steps, slow in her movements.

VIII. *Substance* 1956.



3, 5-dimethoxy-, 4-benzyloxyphenyl-aethyl-amine.

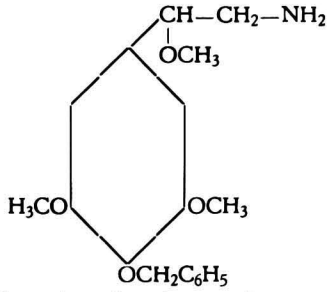
Light gray cat. Weight 3.25 Kg. Tame and quiet, not easily injected. The injection proceeds with little or no reactions of pain.

3.15 Injection 200 mg of substance 1956.
Walks about in her usual manner, somewhat restless.
3.30 Motility normal.
3.45 The same.
4.00 The same.
4.15 The same.
4.35 Stands upright for a considerable time against the bars, as she has been placed against them, then assumes an unusual posture with her head on one side and her mouth wide open, slow in her movements, little reaction to touch.
4.55 Standing against the bars for some time, then assumes an abnormal attitude.

5.10 Looks round, makes sudden movements, sometimes sits with her mouth open. Stretches one paw, moves tardily, hangs on the bars for a moment, then jumps clumsily on the floor, looks fixedly in different directions, makes unwarranted movements of defence, responds little to sounds and touch, is not paralysed, looks fixedly in a certain direction, without an object being visible there.

5.30 Pricks her ears and listens in different directions, lies flat on the floor, dyspnoea, offers little resistance.

IX. *Substance* 1957.



3, 5-dimethoxy-, 4-benzyloxyphenyl-, β-methoxy-aethyl-amine.

Black cat N⁰. 1. Weight 2.25 Kg. Lively and tame. Easily injected. Injection not painful.

3.45 Injection of 100 mg of substance 1957.

3.50 Salivation. Stands in the attitude in which she is placed, hangs on the bars. When startled, she jumps on the floor and sits down in a corner, walks and jumps well, but not spontaneously.

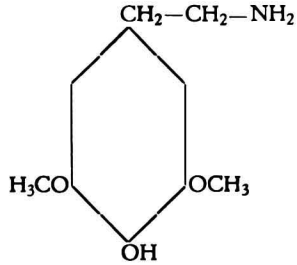
4.00 Vomiting. Afraid, shrinks if approached. Stands for a long time in the posture in which she has been placed. Stands also spontaneously on the hind legs and pricks her ears in different directions. Polypnoea.

4.10 Hangs spontaneously on the bars, then jumps on the floor, walks stiffly and stands again on her hind legs against the wall. Pronounced catalepsy.

4.20 Convulsions of the 4 extremities, first quick, then slow. Wide pupils, afterwards narrow pupils. After the convulsions are over for a moment, she still remains for a while in the attitude, in which she has been placed.

4.30 Convulsions vita minima.

X. *Substance* 1958.

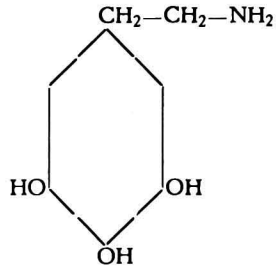


3, 5-dimethoxy-, 4-oxyphenyl-aethyl-amine.

Black cat. Weight 3.75 Kg. Tame and lively, easily injected. Injection not painful.

3.40 Injection of 200 mg of substance 1958.
4.00 Motility normal.
4.10 Hangs for a moment on the back of a chair, then jumps on the floor again in an ordinary way.

XI. *Substance* 1959.



3, 4, 5-trioxyphenyl-aethyl-amine

Gray cat N⁰. 7. Weight 3.3 Kg. Tame and quiet, easily injected. Injection not painful.

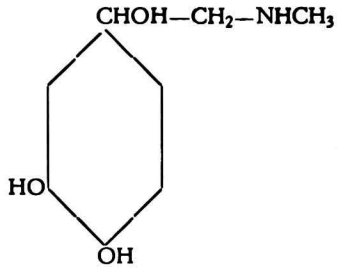
3.40 Injection of 100 mg of substance 1959. After the injection afraid, afterwards quiet.
3.50 Slightly retarded, sits quietly in a corner.
4.00 Standing for a moment in the attitude in which she has been placed, then sits down quietly in a corner. Slow. Walks and jumps well.
4.10 Hangs on the bars for a considerable time, stands in the posture in which she has been placed, then slowly reassumes the ordinary posture, walks spontaneously slowly and shrunk up. Objects to change of attitude (negativism). Responds to the surroundings.
4.20 Sits fearfully shrunk up. Does not stand in the posture in which she has been placed, responds to the surroundings, but slowly. Motility retarded.
4.30 Still slow, hangs on the bars for some time, then jumps on the floor in a normal manner, and sits down quietly. Tendency to retain the same attitude. Responds to loud sounds, slightly fearful, but does not run away.

Thus far the varieties of mescaline, several of which consequently more or less produced phenomena of experimental catatonia, and of which substance 1949 showed this action most distinctly, perhaps even more strongly than mescaline itself.

We now proceed to the examination of some derivatives of adrenaline,

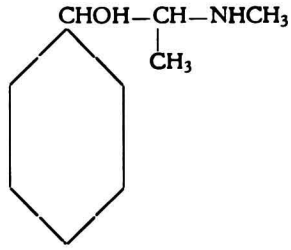
which, according to the investigations of DE JONG [1]), produces catatonic phenomena in a very large dose, lying closely to the fatal one. Only a few

Adrenaline.



orientating experiments on mice have been carried out also by this author with the undermentioned derivatives ; systematic research, however, follows below :

1. *Ephedrine.*



phenylpropanol-, α-methyl-amine.

Black and white cat. Weight 4 Kg. Tame, quiet, easily injected. Injection not painful.

5.00 Injection of 250 mg of Ephedrine. First highly afraid.
5.10 Retardation, tremor of the head, jumps and walks well, slightly afraid.
5.20 Her hairs are on end, she pants, polypnoea. Sits perfectly still, jumps well if approached, stands for some time in the attitude in which she has been placed, hangs for a while on the bars.
5.45 Retarded ; hangs on the bars, stands in the same posture, pants, salivation. Pupils react. Offers resistance when taken up.
6.00 Pants, does not hang on the bars, but jumps on the floor.

Conclusion : Catalepsy.
At night wild with fear.
Two days later still slightly afraid.
Conclusion : Catalepsy present.

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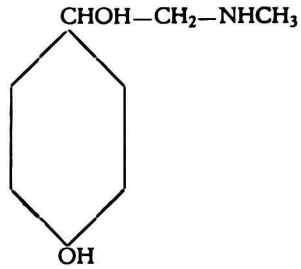
[1]) H. DE JONG : "Hormonale experimenteele Katatonie". Proceedings Kon. Akad. v. Wetenschappen, Amsterdam, **44**, N⁰. 4, 1931.

——————— "Die experimentelle Katatonie als vielfach vorkommende Reaktion des Zentralnervensystems". Zeitschr. f. die ges. Neur. und Psych. 1932. l.c.

2. *Sympathol.*



The second substance of this group was sympathol, which only showed very slight catalepsy and negativism, besides autonomic phenomena, as appears from the protocols below.

Black cat N⁰. 7. Weight 3.75 Kg. Lively, tame.

3.35 Injection 200 mg of sympathol. Afraid, wants to leave the room.
3.45 After sitting quietly she hides spontaneously in a corner. Afraid, offers resistance when taken up.
4.05 Still sitting shrunk up in a corner, offers resistance, allows herself to be stroked, fearful.
4.15 Offers strong resistance (negativism, active and passive), opposes and holds on to things. Resists being pushed on. Does not stand in the same posture. Rather slow in her movements.
4.25 Remains long in the same posture, reacts affectively, objects to being taken up. Does not spit or mew. Moves little and hides spontaneously.

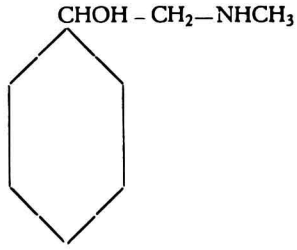
Conclusion : Fear, negativism and transient catalepsy.

Gray cat. Tame, quiet, easily injected. Injection not painful.

10.40 Injection 300 mg of sympathol.
10.50 Salivation, maximally wide pupils, little or no reaction, sits quietly in a corner. Walks and jumps well, spontaneously changes her posture slightly.
10.55 All at once takes a jump, then stands perfectly still for a time, her hairs on end, only moves her head. Staring look.
11.05 Suddenly goes off at a trot, stands still with her hairs on end and immovable tail, salivation, hangs on the bars for a while, then jumps down quickly and lightly. Offers slight resistance when taken up. Stands for a time in the posture in which she has been placed. Pupils maximally wide, not reacting.
11.20 Sits still, moves hardly spontaneously, but more than before, stands no longer in the posture in which she has been placed.
11.30 Pupils slightly narrower, react again. Hairs on end. Sometimes she walks spontaneously.

Conclusion : Indication of catalepsy and negativism, with autonomic phenomena.

3. *Nor-sympathol.*



The third substance of this group was nor-sympathol. It only caused fear and lack of motility, of which the following protocol gives an example.

Lively cat, 3.2 Kg. Easily injected. Injection not painful.

3.40 Injection 100 mg of nor-sympathol. Goes into a corner, moves normally, does not stand in the posture which she has been given. Allows herself to be stroked, is still slightly afraid, moves spontaneously.

4.15 Injection 150 mg of nor-sympathol. Sits down in a corner, looks round, at once takes her usual place after she has been startled. Walks in an ordinary manner, somewhat afraid.

4.30 Motility normal. No resistance.

4.35 As before, slightly retarded in her movements. Jumps slowly from the table on which she has been placed, stands a little longer than usual on a chair against the back, does not offer resistance.

4.40 If she is thrown down, she walks slowly to a corner. Hides, reacts affectively, allows herself to be placed for a short time upright on a chair ; then jumps on the floor again.

4.45 Pronounced tendency to hide, allows herself to be stroked, slow in her movements, accelerated respiration.

4.55 Moves the head a little more.

5.05 Moves again spontaneously, motility still slightly retarded.

Conclusion : Fear and lack of motility.

Summarizing we can say of this group of substances that they could more or less superficially show some phenomena of experimental catatonia.

As *final conclusion* may be stated that the above-mentioned series of investigations confirms the fact, discovered in this laboratory, that experimental catatonia represents a frequently occurring form of reaction of the central nervous system [1]). The problem, whether there would exist a chemical, "catatonizing nucleus" is not yet solved. Further experiments in this direction will be undertaken in our laboratory.

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[1]) Cf. e.g. H. DE JONG : "Die experimentelle Katatonie als vielfach vorkommende Reaktionsform des Zentralnervensystems". Zeitschr. f. d. ges. Neur. u. Psych. 1932, l.c.
——— Annales Médico-psychologiques. 1933, l.c.