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Medicine. — *On the so-called interruption of bulbocapnine-catatonia by means of a mixture of carbon dioxide and oxygen.* By H. DE JONG. (From the psychological laboratory of the Valerius clinic and the Free University Prof. L. VAN DER HORST.) (Communicated by Prof. B. BROUWER.)

(Communicated at the meeting of October 27, 1934).

Experimental catatonia appeared to us[1]) to be a frequently occurring form of reaction of the central nervous system. First we have, together with BARUK[2]), described the syndrome of experimental catatonia for the bulbocapnine reaction. Later on we observed that many other substances may produce catatonia within part of their dosage area. The electric current also appeared to be able to produce such actions under certain circumstances. From our experiments on asphyxial catatonia[3]) it became apparent that carbon dioxide can also produce catatonic phenomena in some experimental animals, namely in mice. The mouse is put in a test glass, into which CO_2 is introduced; the animal is affected with dyspnoea and after a while she shows clonic-tonic contractions. The animal is now taken into the

1) H. DE JONG: "La catatonie expérimentale comme réaction fréquente du système nerveux, etc.". Annales médico-psychologiques. N°. 2, 1933.

2) ———— et H. BARUK: "La catatonie expérimentale par la bulbocapnine". Paris, Masson 1930.

3) ————: "La catatonie expérimentale par des substances gazeuses". Psych. en Neur. Bl. Nr. 3/4, 1934.

fresh air and in some cases a stage may be observed, in which fine complex hyperkinesiae dominate the picture. At the slightest stimulation the mouse takes great jumps, revolves round her longitudinal axis, etc. Then a stage of normal motility appears, followed by a fine catalepsy. The animal may be hung on a thread by two legs, without erecting herself; placed on a bar she stands immovable, even if she has her tail pinched several times. The whole syndrome of experimental catatonia thus develops in reverse order to that of catatonia as it is obtained by means of injection, for example, with bulbocapnine. Here we find: first catalepsy and then, upon increase of the dosage, hyperkinesiae, changing upon still further increase of the dosage into tonic-clonic convulsions (epilepsy). Autonomic phenomena, (an accelerated respiration occurring also in CO_2-catatonia,) complete the picture.

KAUFMANN and SPIEGEL [1]) now describe that bulbocapnine-catatonia in cats is interrupted during 5—10 minutes, if the animals are made to inhale a carbon dioxide-oxygen mixture. Their experiments were inspired by the work of LOEVENHART, LORENZ and WATERS [2]) on what these authors termed "cortical stimulation" by administration of CO_2, for example, to stuporous patients. A combination with oxygen took place; first with 10—15 % CO_2; the respiration was then accelerated, and subsequently the CO_2 dose was increased with 5 % each minute until a concentration of 30—40 % had been reached. The stuporous patients were said to wake up from their stupor during 2—20 minutes, which, among other things, became apparent by their starting to talk in that time.

SOLOMON and KAUFMANN [3]) improved the method and noted the above-mentioned action chiefly in the manic-depressive stupor, sometimes in the schizophrenic stupor as well.

We have now raised the question how this action may be explained. A carbon dioxide-oxygen mixture would be able to interrupt a stuporous state in man, and in the experiment on animals the same might occur in bulbocapnine-catatonia.

In a series of experiments on mice, rats, cats, and a monkey we have now in the first place tried to find out whether we have to deal here with an action of the oxygen or of the carbon dioxide. We have namely brought forward a theory of cellular asphyxia [4]) as one of the possible explanations of the catatonic syndrome. It might be that it is the oxygen which acts here as a direct antagonist. The second possibility is that the carbon dioxide exerts the above-mentioned action. It would be necessary then at the same

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1) M. R. KAUFMANN and E. A. SPIEGEL: "Zeitschr. f. die ges. Neur. u. Psych. Bd. **127**, 1930, S. 312.

2) A. S. LOEVENHART, W. F. LORENZ and R. M. WATERS: Journ. of Amer. Med. Assoc. **92**, 1929, p. 880.

3) SOLOMON and KAUFMANN: Proc. Boston Soc. Psychiatr. May 1929.

4) Katatonie als motorisch physiologisch grondphenomeen op de basis van cellulaire asphyxie. Ned. T. v. Gen. 1933, bl. 2144—2145.

time to explain how carbon dioxide, which itself can produce catatonic phenomena, can interrupt, for example, bulbocapnine-catalepsy.

A first series of experiments shows the phenomenon of a temporary occurrence of normal motility, if an animal, made cataleptic with bulbocapnine, is treated with CO_2 and O_2 (50 % of each). A protocol of such an experiment on a cat follows here:

White cat. 27th October 1933.

10.30 Injection of 100 mg of commercial bulbocapnine.

10.40 Properly cataleptic, hangs on to the edge of the table. Placed in a bell-glass; CO_2 and O_2 are supplied. After some minutes tonic-clonic convulsions occur. The animal is taken into the fresh air. She falls on her side, still twitches for some minutes, recovers and *then walks spontaneously and reactively for about 10 minutes.* When after that she is hung on the edge of the table, it appears that complete catalepsy exists again. Come down on the floor, the animal does not walk either, stands immovable, is again completely catatonic.

11.30 The animal has spontaneously recovered, begins to walk slowly. A second injection of 50 mg is given.

11.47 Is not yet so strongly cataleptic as before.

KAUFMANN and SPIEGEL had for some minutes during a similar experiment observed prompt reaction to stimuli; in our experiment also an interruption of the catalepsy occurred for a short time to such an extent that the animal walked normally, but then relapsed into catalepsy.

The last-mentioned authors further only published a protocol about cats. No experiments were published about the "antagonistic" action on other animals.

We extended our experiments also to mice and monkeys. With mice we did not succeed in demonstrating such an effect. One of these protocols runs as follows:

O_2 and CO_2.

Mice, 13th October 1933.

3 mice, 1 black and 2 white ones, are injected with 1.5 mg of phosphas bulbocapnini.

After 5 minutes a fine catalepsy.

The animals are now placed in a glass cylinder, into which CO_2 50 % and O_2 50 % have been introduced.

The animals become unconscious, are dyspnoeic.

After recovery they are *just as cataleptic as before.*

Conclusion: No influence of the CO_2/O_2 mixture.

With the monkey the results were as follows:

17th November 1933. Monkey of 3.5 Kg (macacus cynomolgus).

11.20 Injection of 75 mg of phosphas bulbocapnini.
11.30 Is not yet completely cataleptic; walks spontaneously.
11.34 Is now completely cataleptic. The animal is placed in a bell-glass.
11.40 A mixture of O_2 and CO_2 (c. 50 % of each) is introduced.
11.43 Some convulsions occur; the animal is at once taken out of the bell-glass, *spontaneously takes a jump.*
11.45 Is again completely cataleptic.
11.50 The same experiment is repeated.
11.55 Clonic twitchings occur. The animal lies on his side and is taken out of the bell-glass; he exhibits a "crucifixion attitude", drops off his legs, *takes a few steps.* Immediately afterwards the animal is again negativistic, resists being pushed forward, after which, however, a few steps follow again.
12.05 Placed on the table, the animal offers resistance, *jumps from the table,* but after coming down he stands cataleptically with one leg fixed against the edge of the table. Salivation and flexed attitude are distinctly present; sometimes there is a sligt tremor of the head.
12.10 Is entirely immovable in the posture of the "Penseur de Rodin". When pinched in the tail, he still turns round for a moment.
12.15 Reacts no longer to pinching in the tail.
Conclusion: The catalepsy has been temporarily interrupted here.

The following protocol shows that great care should be taken not to draw hasty conclusions in case of the monkey. At a low dosage of bulbocapnine the catalepsy in this experimental animal is namely more transient than in cats at a corresponding dose. The catalepsy may then be interrupted by other stimuli as well:

The following is the relevant protocol, when the animal was excited by being put in the narrow bell-glass.

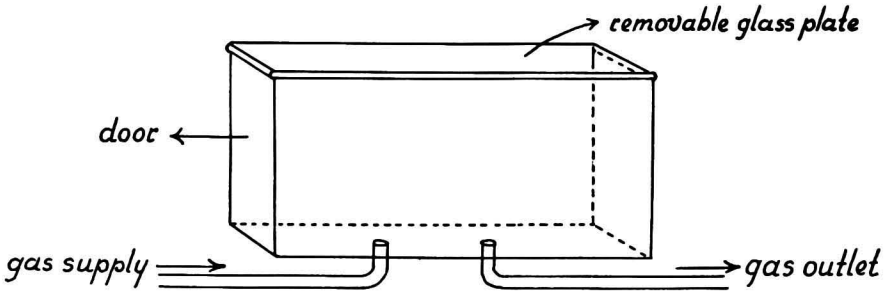
10th November 1933. *Experiment on a monkey, injected with bulbocapnine, with a mixture of* CO_2 *and* O_2.

Macacus rhesus, body weight 3.4 Kg.

10.44 Injection of 50 mg of phosphas bulbocapnini in a long dorsal muscle.
10.54 A fine catalepsy with salivation and occasionally a very slight tremor of the head.
11.00 is placed in the bell-glass, is then very negativistic.
11.04 The introduction of an equal mixture of CO_2 and O_2 is on the point of being started, but the animal is first taken out again for a demonstration of the catalepsy and appears now to have a practically normal motility. The animal runs off but, left alone, he sits down with strongly crooked back. *The motility is practically normal.* The experiment is now discontinued. Not until after ten minutes the catalepsy is restored.

The amount of bulbocapnine, which had been injected, was evidently too small. In order to prevent excitation, due to putting in a narrow bell-

glass, the monkey was placed during further experiments in a special cage, a section of which, speaking for itself, is here reproduced.



A. Experiments on a normal monkey.

First the action of carbon dioxide only, on the normal monkey is investigated. The result appears from the following protocols:

Short action of CO_2.

8th December 1933. Monkey, macacus rhesus, 3.4 Kg, is placed in the glass cage.

CO_2 is supplied.

After about five minutes the animal is affected with dyspnoea, takes a few jumps, is taken out into the fresh air and there almost immediately regains his normal motility.

Conclusion: Dyspnoea, then normal motility during recovery.

Then the CO_2 *is introduced for a longer time*:

10.45 Monkey, macacus rhesus, 3.4 Kg. CO_2 is supplied for a longer time.
10.50 The animal drops off his legs; shows the crucifixion attitude, lying prostrate with the forelegs across on the floor.
10.52 The animal, highly dyspnoeic, falls on his side.
10.53 When he is taken out into the fresh air, his legs appear to be entirely flaccid. The animal also shows salivation.
10.56 The monkey recovers quickly, gets into a stage of excitation, takes great jumps, runs about the room, jumps against the window panes.
11.03 The motility now becomes normal and remains in that condition.

Conclusion: Abnormal postures, finally narcotic condition, paresis. When the animal was taken into the fresh air, first an excitation-stage occurred with hyperkinesia and afterwards normal motility.

Then the experiment was repeated. At first, however, a mixture of *carbon dioxide and oxygen* was administered to the normal monkey. The animal only showed accelerated respiration and no further effect. The introduction of oxygen was now discontinued, so that again only carbon dioxide was administered.

For a short while paresis in the legs was observed, then epileptiform

attacks with tonic-clonic convulsions. When the animal was taken into the fresh air, enormous hyperkinesiae manifested themselves in the form of great jumps. After that the motility became normal again.

In the third place the effect of *oxygen only* on the normal monkey was investigated.

22nd December 1933. Monkey, macacus rhesus, 3.4 Kg.

10.35 Motility normal.
Is placed in a glass cage. *Pure ogygen* is introduced.

10.55 The motility of the animal remains normal.

B. Then *experiments* were made *on the monkey, injected with bulbocapnine*. First the effect of *oxygen only* during the cataleptic stage was investigated :

22nd December 1933.

11.00 Injection of 75 mg of phosphas bulbocapnini.

11.10 Highly cataleptic and negativistic ; salivation, occasionally a slow tremor. Then oxygen is administered.

11.30 The animal remains completely in hypokinetic-catatonic condition.

Conclusion : Oxygen only does not affect the cataleptic condition of the monkey.

Secondly the effect of *carbon dioxide only* on the bulbocapnine-monkey was investigated :

12th January 1934. Monkey, macacus rhesus, 3.4 Kg.

10.40 Injection of 80 mg of phosphas bulbocapnini.

10.50 Completely cataleptic and strongly negativistic, with salivation.

10.55 Introduction of carbon dioxide.

10.58 Tonic-clonic convulsions occur.

11.00 Taken out of the cage, the animal shows spreading of the forelegs (crucifixion attitude), the hind legs lying slack by the side of the body.

11.15 The animal is again normally cataleptic, in side position as well as standing.

Conclusion : Carbon dioxide occasioned paresis and tonic-clonic convulsions, superposed upon the cataleptic condition. Normal motility was not observed.

Thirdly we investigated the effect of a *carbon dioxide-oxygen mixture* (50 % of each) on the cataleptic monkey.

Monkey, macacus rhesus, 3.4 Kg. 19th January 1934. Before the experiment it is ascertained that the motility is perfectly normal.

10.45 Injection of 75 mg of phosphas bulbocapnini.

11.00 Complete catalepsy with negativism, salivation, etc. The monkey is placed in the glass cage.

11.05 Introduction of the mixture of CO_2 and O_2 in the cage (50 % of each).

11.10 The animal drops off his legs in crucifixion attitude.

11.12 Sudden occurrence of violent tonic-clonic convulsions.
11.15 The animal is taken out of the glass cage into the fresh air.
11.25 The convulsions decrease. The animal is lying on his side with the hind legs under the body and the forelegs across on the body.
11.45 The animal becomes gradually stronger and again exhibits the same catalepsy as before the introduction of the carbon dioxide-oxygen.

Conclusion: Paresis and epilepsy, superposed on bulbocapnine-catalepsy by O_2 and CO_2. No normal motility is observed.

This experiment was repeated three times on other dates, always with the same result.

Finally we here mention the result of some *experiments in 2 cases of human catatonia, where a mixture of CO_2 and O_2 had been administered.* In both cases no effect whatever on the catatonic mechanism was to be perceived. We here insert the protocol of one of these experiments (repeated several times with either patient):

15th March 1934.

Patient X. Dementia praecox. Lies in bed in a stuporous condition. Slightly cataleptic and negativistic. Does not reply to questions. A mixture of carbon dioxide and oxygen in the ratio of 50 %—50 % is administered by means of a large funnel, placed on the face and connected with a tube which via a *T*-shaped piece runs to the gas-cylinders. After a quarter of an hour and half an hour respectively the condition is still unaltered, i.e. no answer is given to questions.

22nd March 1934.

The same experiment is repeated. The patient is now more in an excitation stage; he lies quietly in bed but at the slightest stimulation he gets up, shouts and tries to fight. With the help of some assistants he is fixed. Now the mixture of CO_2—O_2 is supplied. After 20 minutes the condition is still exactly the same.

Conclusion and summary: Our series of experiments, carried out for many years, concerning experimental catatonia, made us also consider the problem of a possible anti-catatonic action.

In the first place we investigated in how far a mixture of CO_2 and O_2 might exert a really antagonistic influence on catatonic conditions.

Communications in the literature on the interruption of a stupor during 2—20 minutes by CO_2 and O_2 (LOEVENHART, LORENZ, WATERS, SOLOMON, and KAUFMANN), in addition to a similar action in case of bulbocapnine-catatonia in cats (KAUFMANN and SPIEGEL) led us to this investigation.

In two patients we did not find any effect on the catatonic condition. In case of bulbocapnine-catatonia of some cats we could for some minutes observe some normal walking movements after administration of a

CO_2—O_2 mixture, in the monkey in the greater part of numerous experiments only a mixture of hyperkinesiae, superposed on the bulbocapnine-catalepsy. In one case only we noticed some normal walking movements after administration of CO_2—O_2 to a cataleptic monkey. We also could point out by means of systematic research that CO_2 and not O_2 is the agent which alters the motility, while CO_2 and the mixture of CO_2 and O_2 in monkeys both appeared to provoke the same hyperkinesiae, superposed on the bulbocapnine-catalepsy.

In previous investigations, particularly on mice, we have been able to show that in these experimental animals CO_2 also can produce the complete catatonic syndrome, i.e. catalepsy as well as hyperkinesia.

Our final conclusion now is that in case of the action of CO_2 on bulbocapnine-catalepsy we have not at all to deal with a real antagonism to bulbocapnine.

The same hyperkinesiae, shown by the bulbocapnine-monkey under the influence of CO_2, are also exhibited by this experimental animal if CO_2 is supplied without bulbocapnine. Moreover, we pointed out before that bulbocapnine itself, at a higher dosage than is required to cause catalepsy, also provokes hyperkinesiae, which hyperkinesiae perfectly agree with those caused by CO_2-administration.

It is besides a well-known fact that the dose in between the one causing catalepsy and the one producing hyperkinesiae may sometimes occasion a state of equilibrium between catalepsy and hyperkinesia, in which case the motility is normal. The influence of CO_2 and of the mixture of CO_2 and O_2 respectively may, in our opinion, be put on a level with this.

The gas mixture thus does not act as an antagonist to bulbocapnine, but as bulbocapnine itself upon administration of a larger dose than the one producing catalepsy.

Neurology. — *Preliminary Investigation concerning the Representation of the Fovea in the External Geniculate Body of the monkey.* By S. BRODY, M.D. Yale University, New-Haven. (From the neurological and ophthalmological laboratories of the University of Amsterdam). (Communicated by Prof. B. BROUWER).

(Communicated at the meeting of October 27, 1934).

I. *Introduction.*

A panorama of the development of our present day knowledge of the anatomy of the visual system can be obtained by reference to the work of VON MONAKOW (10), HENSCHEN (7), MINKOWSKI (9), WINKLER (13), RÖNNE (12), BROUWER and ZEEMAN (2), POLJAK (11), DEUTSCH (5), HECHST (6), BALADO and FRANKE (1), CLARK and PENMAN (4) and others.