

THE  
JOURNAL OF MENTAL SCIENCE

[*Published by Authority of the Royal Medico-Psychological Association.*]

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No. 416 [NEW SERIES  
No. 380]

JULY, 1953.

VOL. 99.

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Part I.—Original Articles

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THE PHYSIOLOGICAL BASIS OF THE CARBON DIOXIDE THERAPY  
OF PSYCHONEUROSES.\*

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[Received 23 February, 1953.]

THE present investigation belongs to a series of studies (1) in which an attempt has been made to contribute to an understanding of the mechanisms underlying those forms of therapy of mental diseases which directly involve physiological mechanisms.† In the previous work an experimental analysis was performed in order to determine the common factor involved in the various forms of so-called shock therapy. It was found that all forms of this therapy produced in the experimental animal an increased reactivity of the centres of the sympathetic system to direct (2) and reflex stimulation (3). Chronic experiments (4) also showed that these alterations in autonomic reactivity persisted for a long period of time if the "therapy" (e.g., electroshock) was applied repeatedly as it is commonly done in the human patient. Special experiments revealed that increased sympathetic reactivity can be demonstrated in the hypothalamus (5).

These findings implied that the recovery of mental patients following shock therapy may, at least in part, be linked to these functional changes in autonomic centres and particularly to those affecting the hypothalamus. However, before such an interpretation could be accepted several questions had to be clarified.

The first concerns the state of sympathetic centres in patients who apparently benefit by shock treatment. Since the sluggishness of sympathetic reactions, especially of those which apparently involve supraspinal centres, has been emphasized (6) as one of the important functional characteristics of

\* These studies were aided by a contract between the Office of Naval Research, Department of the Navy, and the University of Minnesota. This work was also supported by a grant from the Graduate School of the University of Minnesota.

† Procedures operating through so-called psychological processes (psychotherapy, etc.) are not discussed in this paper.

schizophrenic individual the action of shock therapy to increase central sympathetic responsiveness seems specifically directed against a functional deficiency of the central nervous system in these patients. But even if this inference is granted it is necessary to show that central autonomic reactions are intimately related to the disease process. Fortunately, the answer to this question is not solely based on the circumstantial evidence that in some schizophrenics symptoms of diencephalic origin appear, and that emotional disturbances suggesting hypothalamic involvement invariably occur but is supported by direct experimentation. Funkenstein, *et al.* (7), found in a large number of mental patients who had been tested with mecholyl, that an improvement occurred only in those cases in which the autonomic reactivity was altered in a certain direction. "When the psychological picture changes, the physiological picture changes, and vice versa. They seem to fit as a 'hand into a glove'." Without attempting a physiological interpretation of these reactions in this paper it may be suggested that hypothalamic reactivity and (mental) behaviour are closely associated.

This conclusion is difficult to understand as long as the hypothalamus is considered to be a centre whose activity is only indicated by para- and sympathetic downward discharges. However, the hypothalamus has been found to activate the whole cortex on direct stimulation (Murphy and Gellhorn (8)) and through reflex activation (Gellhorn and Ballin (9)). The importance of this "upward discharge" for conscious processes has been pointed out by the work of several laboratories (10). These investigations make it plausible that shock therapy influences behaviour. In the normal animal such behavioral changes are indicated by effect of repeated insulin comas, electro-shocks and metrazol-induced convulsions on conditional reactions (11).

Emotional disturbances play a major role not only in functional psychoses but also in psychoneuroses. The successful administration of CO<sub>2</sub> in this disease (12) raises the question whether CO<sub>2</sub> acts on the hypothalamic-cortical system. It is the purpose of the present investigation to elucidate this question, and to contribute thereby to the rationale of the therapy of mental diseases as far as it is based on physiological principles.

*Methods.*—In order to broaden the scope of this investigation the experiments performed on cats anaesthetized with "Dial-urethane" or pentothal were not confined to CO<sub>2</sub> in anaesthetic concentrations, but the action of lower concentrations (10–15 per cent.) on the brain was also investigated. The potentials were recorded from cortical areas and the posterior hypothalamus during rest and after administration of CO<sub>2</sub>. In both conditions the action of afferent impulses resulting from optic, acoustic, proprioceptive and nociceptive stimulation was studied. All cats were curarized and artificially ventilated.\*

#### RESULTS. I. THE ACTION OF 10 TO 15 PER CENT. CO<sub>2</sub> ON THE CEREBRAL CORTEX AND THE HYPOTHALAMUS.

It is known that in the unanaesthetized rabbit the effect of certain sensory (optic) stimuli is diminished when relatively low concentrations of CO<sub>2</sub> are

\* Preliminary reports see *E.E.G. Clin. Neurophysiol.*, 1952, 4, 117.

inhaled (13). These effects could be confirmed in the anaesthetized cat. In Fig. 1 the action of 15 per cent.  $\text{CO}_2$  on evoked potentials of the acoustic and visual projection areas is illustrated. The record shows a progressive diminution in the optically induced potentials with increasing duration of the  $\text{CO}_2$  period. Moreover, the potentials decline in amplitude during each period of stimulation in hypercapnia, whereas they remain constant when air is inhaled. The auditory potentials were unchanged in this experiment. This greater sensitivity of the visual than that of the auditory cortex was frequently seen, although the auditory potentials were often reduced in 10 to 15 per cent.  $\text{CO}_2$ . Similar results were obtained in man when the effect of  $\text{CO}_2$  on optic and acoustic sensations was investigated. The threshold for brightness discrimination (14) and for sounds (15) increased under the influence of 5 to 7 per cent.  $\text{CO}_2$ . The duration and intensity of optical after-images was likewise diminished (16).

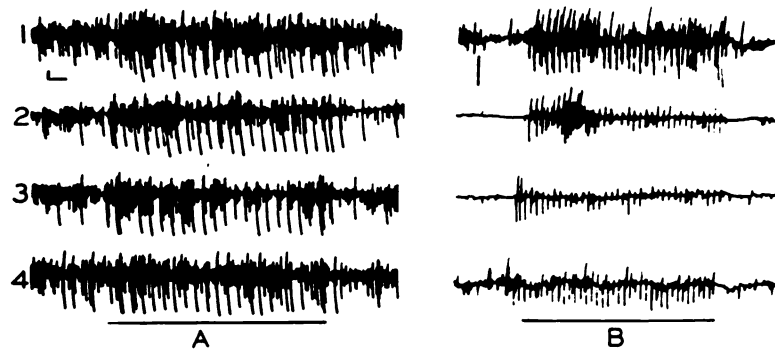


FIG. 1.—Dial cat. E.C.G. of auditory (A) and visual (B) projection area and response to acoustic and optic stimulation respectively. Period of stimulation is indicated by black line. Calibration 30 microvolts and 1 sec. 1, 4 controls; 2, 3 during inhalation of 15%  $\text{CO}_2$ .

One would expect that if the  $\text{CO}_2$  content of the blood were diminished through hyperventilation the reactivity of the cortex would be increased. It was, indeed, found in animal experiments that the responsiveness to sensory stimulation of the specific projection areas of the cortex was augmented during hyperventilation. However, experiments in man do not agree with these observations. During hyperventilation optic and acoustic responsiveness decline (14-16), and sufficiently prolonged hyperventilation may lead to loss of consciousness. These discrepancies become understandable through the following observations, which show that  $\text{CO}_2$  exerts a twofold action on the cortex of the brain.

Although the response of sensory projection areas of the cortex to afferent stimuli is diminished, it is well established that hypercapnia causes excitatory effects on the resting potentials of the cortex. In animals anaesthetized with barbiturates the grouped ("Dial") potentials disappear and are replaced by smaller and more frequent potentials (17). This change in the electrocortico-gram is an indication of increased asynchrony, and comparable to the disappearance of alpha potentials in the human E.E.G. under conditions of sensory stimulation and increased attention. Another sign of increased cortical excitation may be demonstrated on cortical spikes induced by topical applica-

tion of strychnine or other convulsants. Inhalation of 10 per cent. CO<sub>2</sub> leads to an increased spike frequency (Gellhorn and Heymans) (18).

The apparent discrepancy existing between the behaviour of resting and convulsive potentials, and the responsiveness of cortical projection areas to certain sensory stimuli under the action of CO<sub>2</sub>, led to the hypothesis that the former was influenced primarily through a subcortical mechanism which was not essentially involved in the sensory experiments. The following group of experiments seemed to prove the correctness of this assumption:—

Strychnine was applied to two different areas of the left and right cerebral cortex, one of which had been previously undercut through an extensive subpial incision. As Table I shows, only the spikes of the intact cortex reacted

TABLE I.—*Effect of CO<sub>2</sub> on Frequency of Strychnine Spikes in the Normal and Isolated Cortex.*

Cat.	Normal cortex.			Isolated cortex.			Remarks.
	Control.	CO <sub>2</sub> . 1', 3'.	Control.	Control.	CO <sub>2</sub> . 1', 3'.	Control.	
1	58*	174	74	51	36	46	10% CO <sub>2</sub>
2†	63	89	61	13	11	17	"
3‡	68	84	74	25	26	22	"
4	38	56	49§	29	24	23§	15% CO <sub>2</sub>
	43	50	70§	24	12	10§	10% CO <sub>2</sub>

\* Numbers indicate spike frequency per minute.

†, ‡ Cortex undercut 4 and 5 days respectively prior to the experiment. In cat 2 the corpus callosum was also cut.

§ Test made 2 min. after beginning of CO<sub>2</sub> period.

to CO<sub>2</sub> with an excitatory effect (increase in spike frequency), whereas the frequency of the convulsive discharge declined in the undercut cortex (19). Apparently the cortical convulsive discharges are inhibited rather than excited by 10 per cent. CO<sub>2</sub> if subcortical influences are eliminated. One might expect that the effect of CO<sub>2</sub> on non-convulsive potentials would differ fundamentally in the surgically isolated cortex from that seen on the unoperated side, but this question could not be answered, since spontaneous electrical activity in the extensively undercut cortex was minimal.

The next question concerns the origin of the subcortical-cortical discharges which seem to be responsible for the excitatory action of CO<sub>2</sub> on cortical potentials. Since this action of CO<sub>2</sub> is generalized it was thought that hypothalamic-cortical discharges might be involved which under conditions of direct and reflex excitation cause an excitation of the whole cerebral cortex (8, 9). Consequently, action potentials from cortex and hypothalamus were recorded before and during the administration of 10 per cent. CO<sub>2</sub>. If "Dial" potentials were well developed in cortex and hypothalamus it was found that 10 to 15 per cent. CO<sub>2</sub> produced similar changes of asynchrony in cortex and hypothalamus. These phenomena were reversible on readmission of air (20).

The study of the action of certain afferent impulses under the influence of 10 per cent. CO<sub>2</sub> furnishes further proofs for the excitation of the hypothalamic-cortical system in hypercapnia. It was shown by Bernhaut, Gellhorn and Rasmussen (10b, c) that proprioceptive and particularly nociceptive stimulation

causes excitation of the hypothalamus and generalized activation of the cortex. Such stimuli and even those of subthreshold or near threshold intensity become very effective during hypercapnia. Fig. 2 shows the very slight effect of a near threshold nociceptive (heat) stimulus on the cortex under control conditions. There is no change in the potentials of the ipsilateral cortex nor in those of the hypothalamus. However, when this stimulus was applied during inhalation of 10 per cent.  $\text{CO}_2$  a profound effect is recorded in all cortical areas and the hypothalamus. Fig. 2 further illustrates that under these conditions frequency and amplitude (recruitment) is increased, and that the effect persists

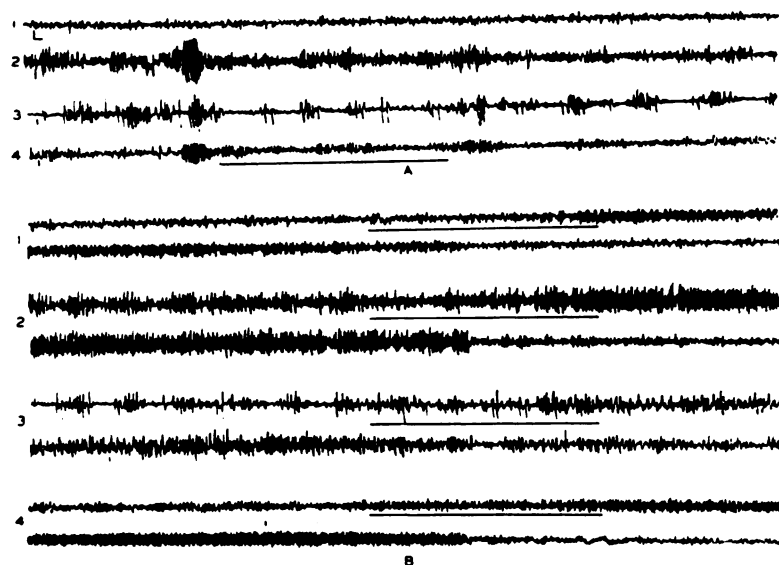


FIG. 2.—Cat, pentothal anaesthesia. Effect of 10 per cent. carbon dioxide on nociceptive stimulation (immersion of right hind leg in water of  $60^{\circ}$  C. for 25 seconds). 1, right hypothalamus; 2, left motor cortex; 3, left gyrus suprasylvius; 4, right motor cortex. A, control, i.e., nociceptive stimulation prior to carbon dioxide. B, nociceptive stimulation during inhalation of 10 per cent. carbon dioxide. The records of the B group start 2 minutes after the onset of hypercapnia. The record 1, 1'; 2, 2'; and 3, 3', 4, 4' are continuous.

for a considerable time after the cessation of stimulation. Similar results are obtained with proprioceptive stimulation in hypercapnia. To summarize:

1. Inhalation of 10 to 15 per cent.  $\text{CO}_2$  induces in the anaesthetized cat an excitation of the hypothalamic-cortical system characterized by asynchrony of neuronal discharge. In barbiturized animals the grouped potentials disappear. These changes occur in the whole cerebral cortex, and are accompanied by similar alterations of hypothalamic potentials.

2. Topically induced convulsive cortical discharges show an increased rate of discharge in hypercapnia. This phenomenon is absent if the cortex is completely undercut in one hemisphere, although the intact cortex shows an acceleration of strychnine spikes during inhalation of 10 per cent.  $\text{CO}_2$ . It is assumed that this rise in the rate of convulsive discharges is due to increased hypothalamic-cortical impulses.

3. The action of nociceptive and proprioceptive stimuli which have previously been shown to excite the hypothalamic-cortical system is greatly aggravated in hypercapnia. Even subthreshold stimuli become effective. The action potentials in cortex and hypothalamus may show not only asynchrony but also recruitment of previously inactive neurons.

4. The effect of optic and acoustic stimuli on their specific cortical projection areas is diminished during hypercapnia in the anaesthetized cat.

*Comment.*—From these observations it may be inferred that cortical activity is modified by at least two systems, the afferent tracts which activate a limited part of the cortex (e.g., the action of visual impulses on their occipital projection area) and the hypothalamic-cortical system which activates the cortex as a whole. Recently it was found that unilateral destruction of the posterior hypothalamus eliminates the excitatory action of CO<sub>2</sub> on the ipsilateral cortex (21). Moreover, the investigations of Magoun and collaborators (10*d*, *e*) and of Bernhaut, Gellhorn and Rasmussen (10*b*, *c*) have shown independently and with widely different techniques that the reticular-hypothalamic-cortical system is necessary for the maintenance of consciousness.\*

The recognition of two fundamentally opposed actions of CO<sub>2</sub> on the brain accounts for certain, apparently contradictory findings reported in the experimental and clinical literature. It is easy to understand that the cortical response to optic stimuli, which is decreased in hypercapnia, is augmented under conditions of hyperventilation. It is also understandable that in the latter state the tone of the hypothalamic-cortical system is diminished to such a degree that large cortical potentials indicative of increased synchrony appear in E.C.G. and E.E.G. That in spite of increased electrical cortical responses to optic or acoustic stimuli during hyperventilation the threshold of perception of such stimuli is increased in the human, appears to be due to the fact that conscious perception depends on the degree of activation of the hypothalamic-cortical system. If the "upward-discharge" from the hypothalamus is decreased, acuity of sensation and perception diminished regardless of the degree of excitation which is indicated in a specific cortical projection area by the action potentials occurring in response to a sensory stimulus.†

It was stated in the introduction that the physiological factor which is common to various forms of "shock therapy" is the action of these procedures to increase the reactivity of autonomic centres, particularly of their sympathetic division. This condition appears to be associated with an increased upward and downward discharge. The action of 10 per cent. CO<sub>2</sub> seems to be similar in principle. The increased upward discharge was demonstrated in the experiments described in this paper. An increased downward discharge was shown to be present in two groups of observations. In the first, the sympathetic division of hypothalamus or medulla was electrically stimulated under control conditions and during inhalation of 10 or 15 per cent. CO<sub>2</sub> and the effect on the blood pressure was recorded. It was found that the pressor response was increased considerably during hypercapnia (22). In the second group, blood

\* For further discussion of this complex problem see Gellhorn, 10*a*, 1*f*.

† On the relation of sensory action potentials to conscious perceptions see Gellhorn (1*f*) (Chapter IX).



pressure, normal and denervated nictitating membrane contractions were recorded in curarized cats prepared under local anaesthesia. Inhalation of  $\text{CO}_2$  produced not only a rise in blood-pressure and repeated and growing contractions of the normal nictitating membrane indicating increasing sympathetic discharges, but also, at the time when sympathetic discharges tended to be large, a contraction of the denervated nictitating membrane (23). This indicates that  $\text{CO}_2$ , in addition, had induced a secretion from the adrenal medulla. Whether inhalation of  $\text{CO}_2$  in non-anaesthetic concentrations may be of therapeutic value in conditions of hypothalamic depression which do not require "shock-treatment" remains to be seen. Experiments are being performed at the present time to heighten hypothalamic excitability by  $\text{CO}_2$  in combination with certain sympathicomimetic amines.

#### RESULTS. II. THE ACTION OF $\text{CO}_2$ IN ANAESTHETIC CONCENTRATIONS (20-40 PER CENT.) ON HYPOTHALAMUS AND CORTEX.

The action of  $\text{CO}_2$  in high concentration was studied in lightly anaesthetized cats. The gas mixtures were made either with air or with pure oxygen but no differences in the effect on the brain were noted. In general, the period of  $\text{CO}_2$  inhalation was confined to 1 to 15 minutes. However, in several experiments it was extended to two hours without producing irreversible effects on brain potentials.

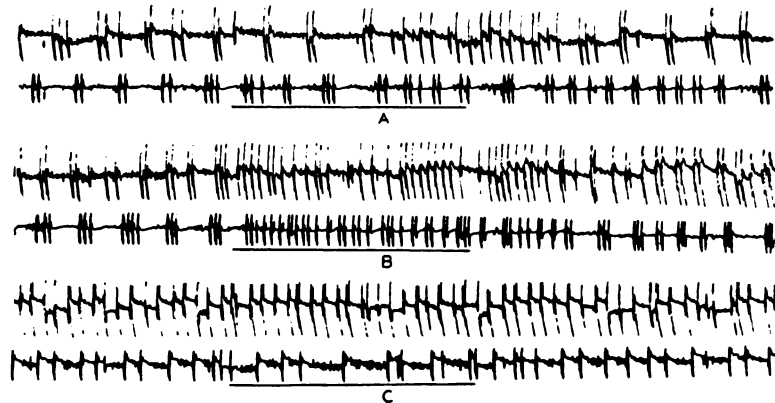


FIG. 3.—Dial cat. Top: left anterior suprasylvian gyrus; bottom: right gyrus marginalis. Both cortical areas are strychninized. Sciatic stimulation (8.2 volts, 100/sec.) indicated by black horizontal line. A, during inhalation of air; B, 40 sec. after onset of inhalation of 35 per cent.  $\text{CO}_2$ ; C, 4 min. 20 sec. after readmission of air. Calibration 100 microvolts and 1 sec.

During the first minute of  $\text{CO}_2$  inhalation slight excitatory effects on the hypothalamic-cortical system may be demonstrated by means of nociceptive stimuli. Thus, Fig. 3 shows on two cortical strychninized areas that a sciatic stimulus which in the anaesthetized cat produced only a slight and rather delayed increase in spike frequency caused an immediate and marked acceleration of spikes in response to the same stimulus applied 50 seconds after the onset of inhalation of 35 per cent.  $\text{CO}_2$ .

Hereafter, typical changes are noted in the electrocorticogram which indicate diminished excitability. These effects appear earlier with increasing concentration of  $\text{CO}_2$ . With 30 to 40 per cent.  $\text{CO}_2$  this effect may occur after one minute, but it may take 3–15 minutes when 20–25 per cent.  $\text{CO}_2$  is applied. The chief effect consists in the elimination of the small and frequent "background"-potentials, while the grouped "Dial"-potentials are hardly altered during this period. As the E.C.G. of the motor cortex in Fig. 4 indicates,

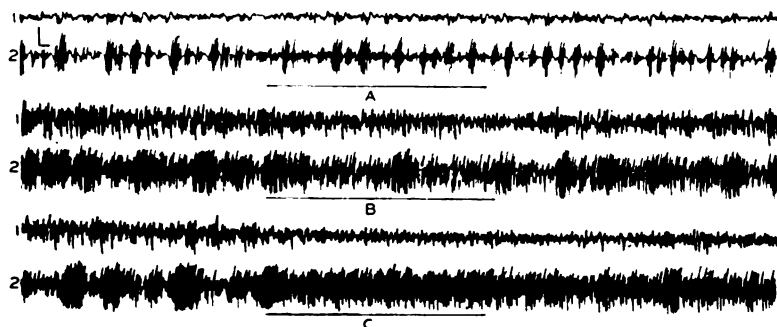


FIG. 4.—Dial cat. Recovery from the action of 35 per cent.  $\text{CO}_2$ . 1, left hypothalamus; 2, left motor cortex. A, after 3 min. in 35 per cent.  $\text{CO}_2$ ; B and C, 3 and 5½ min. respectively after readmission of air. Proprioceptive stimulation (black line) through passive movements of right hind leg. Calibration: 300 microvolts and 1 sec.

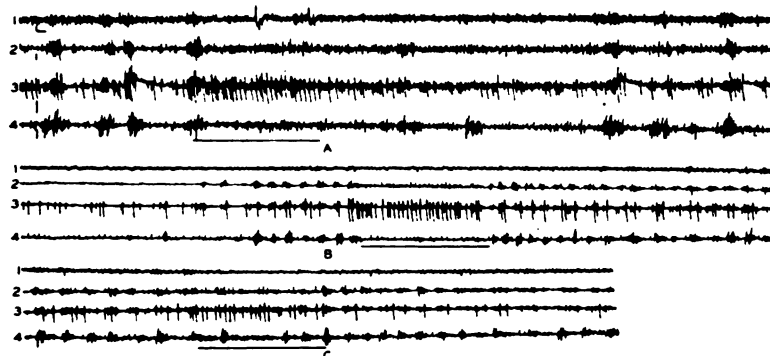


FIG. 5.—Pentothal cat. Effect of proprioceptive stimulation (—) in control (A) and during inhalation of 30 per cent.  $\text{CO}_2$  for 2 min. (B) and 4 min. (C). 1, left hypothalamus; 2, left motor cortex; 3, left anterior suprasylvian gyrus (strychninized); 4, left middle suprasylvian gyrus. Calibration: 100 microvolts and 1 sec.

the effect is apparently opposite to that produced by 10 per cent.  $\text{CO}_2$ , which increases the "background" potentials at the expense of the grouped cortical waves. Occasionally it was found that the "Dial"-groups appeared more frequently during the inhalation of high concentrations of  $\text{CO}_2$  than during the control periods. However, if after these effects have been produced the administration of 30 or more per cent.  $\text{CO}_2$  is continued, the "Dial"-potentials decline in amplitude and finally disappear. Frequently it was noted that several minutes later potentials reappeared in spite of continued administration of  $\text{CO}_2$  (Fig. 5). These potentials consisted of grouped potentials. This



phenomenon is similar to that seen on exposure to low barometric pressure (24).

The recording from the hypothalamus reveals that a rarefaction of the potentials occurs which parallels the diminution of cortical background potentials. Hypothalamic potentials show under these conditions a decrease in amplitude and frequency (Figs. 4, 5). If the CO<sub>2</sub> experiment is carried out to the stage at which cortical potentials disappear it is noted that hypothalamic activity still persists. The effect of high concentrations of CO<sub>2</sub> resembles in this respect the action of anoxia, whose differential influence on cortex and subcortical structures has long been established.

Topically induced cortical strychnine spikes show under the influence of high CO<sub>2</sub> concentrations a decrease in frequency and a slight reduction in amplitude. However, the changes are by no means as conspicuous as the disappearance of the background activity.

The study of the action of acoustic and optic stimuli on their cortical projection areas during inhalation of high concentrations of CO<sub>2</sub> shows that these sensory responses are relatively little altered.\*

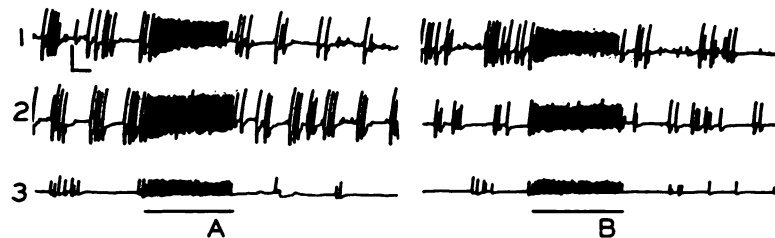


FIG. 6.—Effect of near threshold (B) and suprathreshold (A) acoustic stimuli (clicks) on the E.C.G. of the auditory projection area during control (1), and after inhalation of 30 per cent. CO<sub>2</sub> for 2 and 4 min. (2 and 3 respectively). Calibration: 300 microvolts and 1 sec.

Fig. 6 shows the auditory responses to clicks of two different intensities, the A and B records illustrating the responses to a suprathreshold and near threshold stimulus respectively. It is obvious that with increasing duration of inhalation of 30 per cent. CO<sub>2</sub> the amplitude of the auditory response decreases in this strychninized area parallel with the decline of the size of the strychnine spikes, but no evidence for a rise in threshold was obtained. It was seen not infrequently that the acoustic response was unchanged at a time at which the cortical background-potentials had disappeared. As in the experiments involving "low" CO<sub>2</sub> the responsiveness to optic stimulation was more affected than that to acoustic stimuli. A discrepancy between the behaviour of the spontaneous cortical potentials and the evoked (auditory and visual) potentials was quite common inasmuch as the latter were often recorded at a time at which the spontaneous potentials had disappeared. Fig. 7 is of interest not only as an illustration of the greater sensitivity of the visual as compared to the auditory cortex to "high" CO<sub>2</sub>, but also as a record of hypersensitivity of the cortex to these afferent stimuli on readmission of air (rebound).

\* It should be noted that in order to show the effect of anaesthetic concentrations of CO<sub>2</sub> on the specific projection areas, CO<sub>2</sub> was administered for longer periods than are necessary for the demonstration of profound changes in the reactivity of the hypothalamic-cortical system.

The fact that auditory and visual projection areas retain their responsiveness even to very slight acoustic and optic stimuli in high concentrations of  $\text{CO}_2$  stands in sharp contrast to the cortical reactivity to proprioceptive and nociceptive stimuli under these conditions. It was mentioned earlier that in the lightly anaesthetized animal these stimuli cause a generalized excitation of the cortex

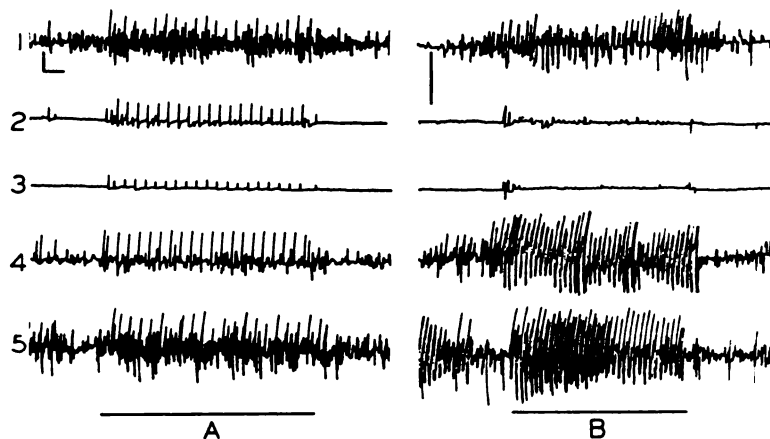


FIG. 7.—Dial cat. Effect of acoustic (A) and optic (B) stimulation on specific cortical projection areas. 1, control in air; 2 and 3, after  $3\frac{1}{2}$  and 9 min. respectively in 35 per cent.  $\text{CO}_2$ ; 4 and 5, 2 and 7 min. respectively after readmission of air. Calibration: 100 microvolts and 1 sec.

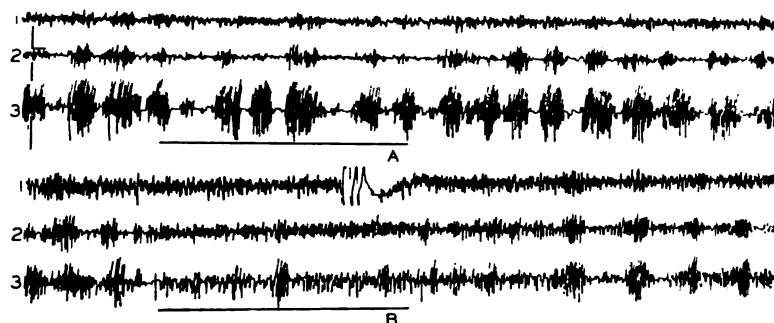


FIG. 8.—Dial cat. Effect of proprioceptive stimulation on hypothalamus (1), left motor cortex (2), and left suprasylvian gyrus (3), during inhalation of 25 per cent.  $\text{CO}_2$  ( $2\frac{1}{2}$  min. after beginning of  $\text{CO}_2$  period), A, and 7 min. after readmission of air, B. Calibration: 300 microvolts and 1 sec.

parallel with that of the hypothalamus. These effects are regularly eliminated in 30 per cent.  $\text{CO}_2$ . Closer study reveals two stages in the action of carbon dioxide: in the first, proprioceptive or nociceptive stimuli still excite the cortex but their action is now confined to the sensori-motor cortex. At the same time the hypothalamus is no longer activated. Thus, Fig. 8 illustrates that after inhalation of 25 per cent.  $\text{CO}_2$  for only two and a half minutes proprioceptive stimulation has no distinct effect on the hypothalamus and the potentials in the suprasylvian gyrus, while a slight excitatory effect persists on the motor cortex, as seen in less frequent occurrence of the grouped ("Dial") potentials. After

readmission of air (B) a distinct excitatory effect of this proprioceptive stimulus is exerted on hypothalamus and all cortical areas. In another experiment, one minute after inhalation of 35 per cent.  $\text{CO}_2$ , a slight but distinct excitatory action of proprioceptive stimulus was noted on the sensori-motor cortex (anterior and posterior sigmoid gyrus), but the potentials remained unchanged in the suprasylvian gyrus. However, before and after the  $\text{CO}_2$ -experiment proprioceptive stimulation exerted a marked excitation on hypothalamus and cortex, which persisted for a considerable time beyond the period of stimulation. The profound changes in the reactivity of the hypothalamic-cortical system which under control conditions accounts for the generalized cortical excitation in response to proprioceptive and nociceptive stimuli occur in "high"  $\text{CO}_2$  at a time when the changes in the acoustic and optic response are slight.

On continuation of the application of  $\text{CO}_2$  even the sensori-motor cortex fails to react and shows no significant changes in grouped potentials in response to these stimuli, although, as was mentioned earlier, minimal acoustic or optic stimuli remain effective.

Fig. 5 illustrates the action of 30 per cent.  $\text{CO}_2$  on resting and strychnine potentials of cortex and hypothalamus and on the responsiveness to proprioceptive stimulation. In part A of this figure (control) the grouped potentials disappear from hypothalamus and cortex during and for some time after the end of the period of stimulation. This is interpreted as an indication of increased asynchrony as the result of excitation. In addition, the potentials recorded in the second and fourth line show an increase in frequency and amplitude of the background potentials indicating recruitment of additional neurons characteristic for strong cortical excitation. The latter is also evident from the increased spike frequency in the third line of section A (Fig. 5).

Section B shows a greatly diminished reaction of the hypothalamic-cortical system after two minutes of 30 per cent.  $\text{CO}_2$ . It will be noted that at the beginning of this section the cortical potentials had almost disappeared, but Dial-potentials returned several seconds prior to proprioceptive stimulation. The latter had a lesser effect than under control conditions. The excitatory effect was confined to the period of stimulation, and no signs of neuronal recruitment are evident. Finally, in section C only traces of cortical excitation are seen.

Fig. 4 gives another illustration of the fact that the proprioceptive action on hypothalamus and cortex disappears completely three minutes after administration of 35 per cent.  $\text{CO}_2$ . Sections B and C of this figure show the gradual restoration of asynchronous excitation and recruitment in response to proprioceptive impulses on readmission of air.

Fig. 9 shows in "high"  $\text{CO}_2$  no significant change in hypothalamic and cortical potentials in response to a nociceptive stimulus which caused a profound and prolonged excitation under control conditions. It is to be emphasized that such stimuli became ineffective during an early phase of the administration of "high"  $\text{CO}_2$  when the cortical potentials are still well developed. This phenomenon is in sharp contrast to the observation that optic and particularly acoustic stimuli remain effective in "high"  $\text{CO}_2$  at a time at which the cortical-potentials are abolished.

It was stated earlier that as the excitability of the hypothalamic-cortical system decreases in "high"  $\text{CO}_2$  the reactivity of the sensori-motor area (sigmoid gyrus) may be retained while other cortical areas do not respond to proprioceptive or nociceptive stimuli. This fact is reflected in the restoration of

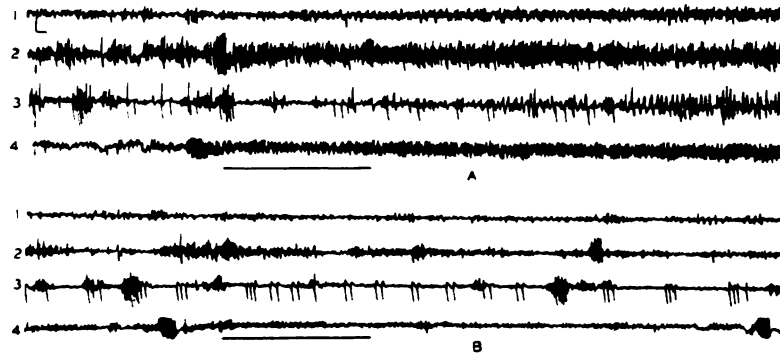


FIG. 9.—Pentothal cat. Effect of nociceptive stimulation (right hind leg in water of  $70^{\circ}\text{C}.$ ) on cortex and hypothalamus under control conditions (A) and after 2 min. of inhalation of 40 per cent.  $\text{CO}_2$ . 1, right hypothalamus; 2, left motor cortex; 3, left gyrus suprasylvius; 4, right motor cortex. Calibration: 100 microvolts and 1 sec.

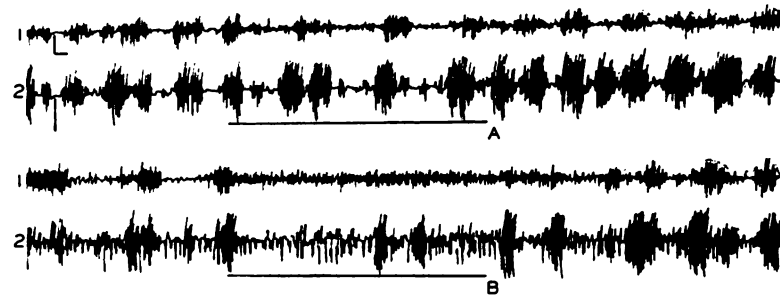


FIG. 10.—Dial cat. Effect of proprioceptive stimulation on left motor cortex (1) and left middle suprasylvian gyrus after 3 min. in 25 per cent.  $\text{CO}_2$  (A) and 8 min. after readmission of air. Calibration: 300 microvolts and 1 sec.

cortical responsiveness to these stimuli after air has been readmitted. Fig. 10 shows that a proprioceptive stimulus had become ineffective on the sigmoid (motor) and the suprasylvian cortex after three minutes of inhalation of 25 per cent.  $\text{CO}_2$ . Some minutes after recovery in air both parts of the cortex react to the afferent impulses. There is, however, a marked difference in the degree of responsiveness of the two areas. The motor cortex reacts with asynchrony plus recruitment (the amplitude of the background potentials is greatly increased), while the suprasylvian area shows only a delay but not a disappearance of Dial-potentials and no evidence of recruitment. Duration and degree of excitation are much greater in the motor than in other cortical areas.

*Comment.*—From this experimental work it is obvious that "high" and "low"\* concentrations act in an entirely different manner on cortical and hypo-

\* These terms are used for the sake of brevity, "high" being synonymous with anaesthetic concentrations, "low" being applied for  $\text{CO}_2$  of about 10 per cent.

thalamic potentials. Whereas "low" CO<sub>2</sub> gives by elimination of the large, grouped potentials and by the appearance of small, fast electrical variations evidence for increased asynchrony of cortical discharges, the changes resulting from "high" CO<sub>2</sub> appear indicative of increased synchrony. The latter is particularly seen when after a period of iso-electricity the grouped cortical potentials reappear at shorter intervals than in the control periods. The absence of the background potentials in "high" CO<sub>2</sub> may be similarly interpreted. The study of hypothalamo- and corticogram further reveals that in sensitive preparations "low" CO<sub>2</sub> causes, in addition, recruitment of previously inactive neurons, whereas "high" CO<sub>2</sub> produces increasing degrees of rarefaction of electrical discharges. The latter seems to be the expression of a progressive decruitment of neurons in cortex and hypothalamus.

A closer analysis shows a parallelism between background-potentials and hypothalamic activity. If the latter is increased as it occurs in "low" CO<sub>2</sub> the background potentials increase in frequency and amplitude, whereas in "high" CO<sub>2</sub> the disappearance of the background potentials corresponds to the rarefaction of hypothalamic discharges. Furthermore, proprioceptive and nociceptive stimuli, which have been shown to induce a generalized cortical excitation characterized by asynchrony (and recruitment) through hypothalamic excitation, have a greater effect on the hypothalamic-cortical system in "low" CO<sub>2</sub> than in the control experiment, and exert no effect in "high" CO<sub>2</sub>. Under these conditions the degree of cortical and hypothalamic excitation runs roughly parallel, and is directly related to the frequency and amplitude of the background potentials and the persistence of these changes beyond the period of stimulation. Finally, the dependence of these potentials on the hypothalamus has been established by the fact that ipsilateral destruction of the posterior lateral hypothalamus eliminates the excitatory action of "low" CO<sub>2</sub> on the ipsilateral cortex as well as the effect of proprioception and nociception on this cortex.

The grouped "Dial"-potentials appear to be of a different origin. They may persist in "high" CO<sub>2</sub> when the responsiveness of the hypothalamic-cortical system to nociception and proprioception is eliminated. The grouped potentials seem to depend on the activity of the intralaminar thalamic nuclei, which are closely related to sleep and other inhibitory reactions. "High" CO<sub>2</sub> as well as barbiturate narcosis functionally eliminate the hypothalamic-cortical system,\* just as surgical lesions in the reticular substance (10ε) of the brain stem which produce increasing degrees of cortical synchrony and coma.

The implications of these investigations for the problem of consciousness are considered elsewhere. It may suffice to discuss their significance for questions of therapy in neuropsychiatric disorders. The experiments have shown the separability of the long tract systems which activate specific cortical projection areas, from the hypothalamic-cortical system which activates the cerebral cortex as a whole. Administration of CO<sub>2</sub> allows one to increase or decrease the reactivity of this system, and what is of particular importance, to alter *pari passu* the degree of the hypothalamic-cortical discharge. This is of great importance, because it must be assumed that this system plays a central role

\* Unpublished observations.

in psychoneuroses as well as in functional psychoses. Whatever the basis of the fundamental differences in the physiological mechanisms may be which differentiate psychoneuroses from psychoses and also account for the various forms of functional psychoses—and the complexity of these problems and the great variety of the factors which are operative are not denied—it seems rather certain that in neuroses as well as in a large group of psychoses emotional disturbances play a decisive part. Translated into physiological concepts, this means that the hypothalamic-cortical system is involved in these disease processes. Carbon dioxide, depending on the concentrations used, may increase or decrease the reactivity of this system. Therefore, CO<sub>2</sub>-therapy and other procedures acting with similar selectivity on the hypothalamus and the “upward” discharge originating in this structure appear of great potential therapeutic value.

It is obvious that the usefulness of CO<sub>2</sub>-therapy depends chiefly on three factors: (1) the point of attack of CO<sub>2</sub> in the central nervous system; (2) the type of change induced by inhalation of CO<sub>2</sub>; and (3) on the duration of this effect. The first two points seem to have been clarified by the present investigations, while experiments on the third problem are urgently needed. Whether CO<sub>2</sub>-therapy is of value remains to be seen. But it is clear from the experimental work described in this paper that “high” CO<sub>2</sub> should be applied only in such patients who show evidence for an increased reactivity of the hypothalamus-cortical system.

The experimental work discussed in this paper was not performed in order to advocate or criticize CO<sub>2</sub>-therapy. It rather aims to develop certain physiological principles and to apply them to problems of therapy in mental diseases. These principles may become guide-posts for selection and application of other therapeutic procedures. With this limitation in mind, certain therapeutic suggestions appear to be in order. Obviously “high” CO<sub>2</sub> should be applied only in such patients who show evidence for an increased reactivity of the hypothalamic-cortical system. Since its effect on the hypothalamic system is related to the duration of the administration of CO<sub>2</sub> and its concentration, and since the persistence of its action is likely to depend on both factors, it may be of importance to reduce concentration and extend the period of CO<sub>2</sub>-administration for prolonged periods of time. Schäfer (25) noted in his experimental subjects that on exposure to 3 per cent. CO<sub>2</sub> for several days euphoria and increased ergotropic effects (“Gefühl einer gesteigerten Leistungsfähigkeit”) occurred on the first day, while symptoms of a diminished excitability and of a lower level of consciousness prevailed on subsequent days. The latter state was described as being intermediate between wakefulness and sleep and was associated with an increase in chronaxie of peripheral nerves. On the contrary, during the phase of increased excitability noted during the first day of exposure to 3 per cent. CO<sub>2</sub> the chronaxie was decreased. These symptoms indicate clearly that in the first phase hypothalamic discharges are increased, while they are diminished in the later stage.

On the other hand repeated treatments with brief periods of “low” CO<sub>2</sub> (perhaps 5 to 10 per cent.) or with several hours of 3 per cent. CO<sub>2</sub> would be appropriate in cases in which the hypothalamic-cortical system is hyporeactive.



These procedures could be aided by simultaneous administration of drugs which would raise hypothalamic excitability. Preliminary experiments on animals suggest that sympathicomimetic amines may be suitable for this purpose.

Selection of the form of therapy and its duration should be guided by physiological tests which before and during the treatment determine the state of the hypothalamus. The important problem concerning a quantitative indicator of hypothalamic reactivity will be discussed elsewhere (26).

#### SUMMARY.

Experiments are reported on the action of 10 per cent. ("low") CO<sub>2</sub> and anaesthetic concentrations of CO<sub>2</sub> (30-40 per cent. "high") on hypothalamus and cortex of the lightly anaesthetized cat. It is shown that "low" CO<sub>2</sub> activates the hypothalamic-cortical system. Carbon dioxide causes an increased asynchrony of the electrocorticogram and augments the frequency of cortically induced convulsive spikes. Nociceptive stimuli which act on the hypothalamic-cortical system are more effective in "low" CO<sub>2</sub> than during control periods. Hypothalamic and cortical changes run parallel and unilateral lesions of the posterior hypothalamus prevent the generalized excitation of the cortex by CO<sub>2</sub> on the side of the lesion.

The increased hypothalamic-cortical "upward" discharge is associated with an increased sympathico-adrenal "downward" discharge, as indicated by the fact that "low" CO<sub>2</sub> induces contractions of the normal and denervated nictitating membranes and a rise in blood-pressure. In addition, the reactivity of the hypothalamus to electrical stimulation is augmented during administration of "low" CO<sub>2</sub>.

Contrariwise, the reactivity of specific cortical projection areas (e.g., visual and auditory cortex) is diminished during CO<sub>2</sub>-inhalation. This indicates that the activity of the cerebral cortex depends on two different systems at least, and that "low" CO<sub>2</sub> specifically increases the responsiveness of the hypothalamic-cortical system.

On the other hand, administration of "high" CO<sub>2</sub> reduces and finally abolishes the reactivity of the hypothalamic-cortical system. This is indicated by the disappearance of background potentials in the cortex while grouped potentials are not markedly affected. At this stage nociceptive and proprioceptive stimuli lose their effect on the hypothalamus and, at the same time, the generalized effect on the cortex disappears. Nevertheless, the reactivity of the visual and auditory cortex to specific afferent impulses is retained. "High" CO<sub>2</sub> may be used to reduce or abolish the reactivity of the hypothalamic-cortical system without eliminating the responsiveness of specific cortical projection areas. The procedure is apparently harmless for the brain, inasmuch as the action of prolonged administration of "high" CO<sub>2</sub> for several hours is completely reversible on hypothalamic- and cortical potentials.

Since the hypothalamic-cortical system is intimately related to emotional processes, it is suggested that "low" CO<sub>2</sub> may be of benefit to patients whose hypothalamus is hyporeactive, whereas the administration of "high" CO<sub>2</sub> appears to be appropriate in cases of hypothalamic hyper-reactivity.

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