HYPERVENTILATION EXPERIMENTS DURING CO₂ AND O₂ INHALATION IN PATIENTS WITH CONVULSIONS.*

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SINCE Foerster's method of hyperventilation taught us how to provoke epileptic seizures in epileptics at will in a far larger percentage than by any other method which could be used clinically, a number of investigations have been conducted in order to find out which of the changes that arise in the organism during hyperventilation must be considered the cause of the fit. Even though there is general agreement that on hyperventilation the epileptic fit is caused by a non-specific factor—and therefore it must not be expected that its study will lead to the discovery of the more intimate pathogenic factors of the epileptic fit—it is all the same of much interest to ascertain to which change the epileptic organism reacts with a seizure when the patient hyperventilates.

Georgi and several others lay the main stress upon the alkalosis which is the result of the intake of CO₂ through respiration, and on the shifting of ions and changes in colloid-chemical conditions in the blood, which take place at the same time. Others, and among these Foerster, put down the primary effect to the change in circulation, especially a vasoconstriction of cerebral vessels. In Denmark Hendriksen has advanced the hypothesis that vasoconstriction during hyperventilation is a reaction to the fall in blood-pressure which practically always takes place and that vasolabile epileptics are the first to exhibit the reaction. Lastly we must reckon with another factor, viz., that the 'psychic trauma' represented by the hyperventilation may play a releasing part, exactly corresponding to the well-known fact that emotional disorder may cause fits in epileptics.

TECHNIQUE.

We have therefore tried whether, by submitting epileptics to hyperventilation under such conditions that alkalosis does not arise, it is possible to prevent the occurrence of fits. If this were the case, it would plead in favour of the idea that the alkalosis is the releasing factor—if fits occurred none the less, the theory of alkalosis might be taken for disproved.

In order to prevent the alkalosis, we allowed the patients to inhale CO₂ in different concentrations. Several investigators have had this idea, but we

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have not been able to find in the literature a corresponding systematic series of experiments, carried out on human material.

We do not consider it a serviceable technique to increase the CO_2 concentration of the inspired air by letting the person reinspire the expired air, as Lennox and Cobb have done a few times. In these experiments one is working with an unknown concentration of CO_2 , and it must also be remembered that an experiment of fairly long duration will cause an anoxæmia, which is not without significance.

For the experiments we have therefore employed an apparatus which we use in cases of carbon monoxide and other intoxications, and which is a completed and somewhat modified Haldane oxygen-apparatus. Through this apparatus a certain concentration of CO_2 is inhaled, the rest being pure O_2 ; the tension is low, it being possible to regulate the delivery in such a way that the accumulation bag is exactly filled in the expiration pause. Through this an overpressure of any significance is avoided, and this is of importance, it being the partial tension of the gases and not their percentage in the air of the alveoli which decides their relative quantity in the blood. Expiration takes place through a valve on the mouth-piece.

We soon came to see that, by letting the patients breathe through a mask, more conditions than those determined by the gases inhaled are changed.

First of all the psychic attitude of the patients towards the experiment is surely different from what it is during simple hyperventilation. Moreover it must be taken into consideration that the conditions of pressure in the thorax, and through these the blood-pressure, are changed during respiration under a certain pressure. Therefore, as a sort of control, we allowed some of the patients to inhale pure O_2 . Thus some have been tested with simple hyperventilation and with CO_2 - O_2 inhalation, others with simple and with O_2 hyperventilation, and some have been tested with all three methods. For other reasons than pure control the testing of hyperventilation during inhalation of pure O_2 is of importance. In their monograph on epilepsy Lennox and Cobb mention—rather en passant—that both by inhalation of O_2 and of CO_2 they are able to prevent hyperventilation from causing fits in one single or some few cases—it looks as though they have not tried with more. It might therefore be maintained that the difference which appeared in our experiments on simple and on CO_2 - O_2 hyperventilation was due to the oxygen in the latter method, and not to the addition of carbon dioxide.

Thus our method has been, either on the same day, or more often at an interval of one or two days, to hyperventilate the person in question with two or three of the methods. At times we first used simple hyperventilation, at other times first one of the other methods, in order to exclude that possible anxiety the first time the experiment was carried out might influence the results. It turned out, however, that the occurrence of fits was quite independent of whether it was the first or second time the patients were examined. Most often the patients were lying down, sometimes they sat up, but this does

not seem to influence the results. The time of day varied, but we have not been able to prove any relation to meals in the cases in which fits occurred. Otherwise the technique was the one generally used for hyperventilation. In the carbon dioxide experiments we used different concentrations—from 5 to 15 per cent., usually about 10 per cent.

On account of irritation of the respiratory centre, an increase in the frequency of respiration takes place during CO₂ inhalation, similar to the increase spontaneously exhibited by the patients during simple hyperventilation, but often somewhat quicker. The patients were asked, as far as possible, to breathe during the inhalations exactly as they did during simple hyperventilation—very deeply and a little quicker than normally, but without any great effort.

RESULTS OF EXPERIMENTS.

We will not describe the course of the experiments in detail; it was the same as has so often been described in recent literature, and a series of the same symptoms as others have described, appeared.

As is always the case at a psychiatric department of the same sort as the clinic for mental diseases at Kommunehospital, the material at our disposal was very mixed. We have examined epileptic cases of a fresh, incipient kind, as well as old, demented cases with typical seizures. We also included a group of patients with doubtful attacks of convulsions, with epileptic 'equivalents,' or with badly observed seizures, in order to reach, perhaps, a diagnostic conclusion. Lastly we included a smaller number of patients with obvious hysterical convulsions, partly because these patients on extraneous provocation so easily give their emotion outlet in the shape of 'convulsions,' and therefore must form an excellent control-material as regards the purely psychical influence of hyperventilation; and partly because we hoped to find amongst them 'emotional epileptics,' corresponding to Guttman's restriction of this conception, and thus get a chance of following these patients under the different experimental conditions. We regret to say that in no case did we succeed in provoking such 'emotional epileptic' fits as Guttman has done several times.

Within our group of epileptics, there are 20 patients in all; 15 cases belong to so-called genuine epilepsy, two are encephalitic, one is definitely and one doubtfully traumatic, and one is due to syphilis of two years' duration, which most likely has caused convulsions through a meningeal process.

As may be seen from fig. 1, in which we have put down our results graphically, we have in all made 71 experiments on 34 patients. In 10 experiments—on seven patients in all—we succeeded in provoking epileptic phenomena. In percentage this approximately corresponds to the results of a series of other investigators of recent years, being about 20 per cent.

The epileptic phenomena which have been put down in the Table as 'fits' are partly convulsions—thrice in epileptics on simple hyperventilation, once in a patient with doubtful epilepsy (the diagnosis *before* hyperventilation);

partly 'absences'—once in an epileptic on simple hyperventilation, twice on O_2 hyperventilation, once on CO_2 inhalation; and lastly, in two experiments with simple hyperventilation, 'psychic equivalents' were provoked in one epileptic, of the same character both times, and resembling similar fits in the *historia morbi* of the patient.

We cannot here enter into the fits of each single patient, or other details. We have of course only counted what we reckoned as definite epileptic mani-

FIG. 1. The experiments placed after the kind of fits and experimental conditions. The columns to the left indicate the number of experiments. The black part of the column marks the number of patients with pronounced tetanic, the streaked part the number of patients with less pronounced tetanic phenomena during the experiment. The columns to the right indicate the number of patients who produced epileptic fits during the hyperventilation experiment. The slender columns farthest to the right show the number of functional reactions.

festations. In most cases the fits have occurred in a period in which the patient had many fits, or at a time when, according to the usual interval between the fits, spontaneous fits might soon be expected, but this rule has not been quite without exceptions. In the patient in whom we most often—in four out of five experiments—provoked epileptic phenomena, these fits were the only ones observed during his stay at the department. At the same time we might mention that this patient had a fit during one of his CO_2 experiments, a result

to which we will return later, and which we will so far keep out of the discussion. *In all other cases fits failed to appear on inhalation of the CO₂ mixture, including patients in whom they otherwise appeared—spontaneously—with great frequency.*

Hence, as may be seen from the Table, this is our chief result: that with CO₂ inhalation it is possible to prevent fits from occurring, while otherwise they appear both on simple hyperventilation (seven fits in 25 experiments on epileptics and on patients with doubtful epilepsy) and on O₂ hyperventilation (two 'absences' in 11 experiments on patients of the same category).

Furthermore, it may be seen from fig. 1 that in a series of cases psychical reactions have been provoked in the patients—most often crying or exaggerated 'functional' exhaustion and lamenting. As was to be expected, these reactions are most frequent in patients with hysteria and in those cases of epilepsy that are doubtful and in which the diagnosis mostly turns towards hysteria. Only once was a psychical reaction provoked in a genuine epileptic—reacting on a tetany fit. We cannot venture, on the basis of so scanty a material, to draw any conclusions as to the differences under different experimental conditions—the reactions are most likely purely unspecific reactions of fatigue.

PHENOMENA OF TETANY.

Before we discuss further the conditions for the appearance or non-appearance of epileptic phenomena during our experiments, we may make a few remarks on the tetany phenomena, which we otherwise will not discuss more in detail in this paper.

It can be seen clearly how the phenomena of tetany—appearance or increase of the facialis phenomenon, paraesthesiae, muscular phenomena, spasms, etc.—occur with great frequency in experiments with simple hyperventilation and with O₂, *but are totally absent in the CO₂ experiments.* Every time we have tested a patient who already had a facialis phenomenon with CO₂ inhalations, Chvostek's sign has decreased or totally disappeared, whilst with the other methods it has never failed to increase considerably.

It cannot be denied that this finding seems to support the alkalosis theory, originally stated by Grant and Goldmann, in which they explain the hyperventilation tetany by alkalosis alone. Without discussing the question in detail, however, we must point out that of course the CO₂ inhalations cause changes in the ion-concentrations different to those caused by simple hyperventilation and by O₂ hyperventilation, and it may be these changes which cause the absence of the tetany symptoms. The Ca-ion during hyperventilation has been examined by several investigators, but the results have often been antagonistic. We will only add that, in agreement with Hendriksen, we have not been able to prove any parallelism between the appearance and intensity of the tetany phenomena on one hand, and the appearance of the epileptic phenomena on the other.

DISCUSSION.

When we turn to the chief problem—what the factor is which is changed during the CO_2 inhalations, and which causes the non-appearance of the fits—we must admit that our experiments only give very little direct information about this—their arrangement and results are meant merely to orientate and are only presented as a preliminary report.

Without a more refined technique, without extensive use of chemical investigations of the composition of the blood during the different experimental

FIG. 2. The blood-pressure during the experiments. The columns indicate the rise or fall of blood-pressure. Black marks patients with fits during the experiment. The columns for each patient are placed in the same vertical line.

conditions, and especially without a large control-material of experiments on normal persons, these experiments will hardly lead to a definite answer to this important question. But it is possible, on the basis of the investigations in hand concerning the general reaction of the organism towards forced respiration, and to inhalation of CO_2 and O_2 , to point out some of the explanations which may possibly correspond to our experiments.

Here we will partly discuss circulation, especially the blood-pressure, partly changes in the composition of the blood.

I. As is seen in fig. 2, in which we have set down the blood-pressure of one group of patients, divided according to the methods of hyperventilation used, we have on simple hyperventilation in by far the greater number of cases found a decrease in blood-pressure, i.e., in 27 out of 33 cases. The decrease in blood-pressure on simple hyperventilation is caused by a series of factors.

Because of the CO₂ ventilation the tonus of the vasomotor centre towards the vessels is decreased (Dale and Evans), it being the general opinion that CO₂ has a specific influence on this centre, as it has it on the centre of respiration (Henriques and Ege). At the same time the decreased tension of CO₂ in the peripheral vessels causes a certain degree of anoxæmia—according to the 'Bohr effect' (cf. Haldane), and from this follows a failure of the peripheral circulation, which has been shown by Henderson by direct observation of the intestinal vessels, and by Stewart in the vessels of the hand by a calorimetric method. This causes a smaller reflux to the heart through the veins, and hence a decrease in the minute-volume. Moreover it is likely that mechanical factors are of importance, at any rate so far as the initial fall in blood-pressure during hyperventilation is concerned. As mentioned, a fall in blood-pressure was found in most of our experiments.

While, however, we are not able to accept the hypothesis of Hendriksen, that the fall in blood-pressure is the direct cause of the epileptic fit during hyperventilation, because it causes a reactive constriction of the vessels of the brain, this is firstly due to the fact that neither in our own nor in Hendriksen's experiments do we find any parallelism between the intensity of the fall and the occurrence of the fits; secondly, because we have seen fits appear simultaneously with a rise in blood-pressure—we must admit this was only seen in one patient but on repeated experiments—and thirdly, because, in spite of the repeated occurrence of fall in blood-pressure in experiments with O₂, we have not seen any fits accompanying this fall. In three patients hyperventilation is accompanied by a rise in blood-pressure—all these patients also show a rise in blood-pressure during O₂ and CO₂ experiments—in one case it was, however, followed by a fall in pressure. Perhaps the divergent reaction of these patients is due to physical factors or to great muscular effort—according to Raab both these factors are able to complicate the effect of CO₂ ventilation. In the experiments with CO₂ we more often find a rise in blood-pressure, as might be expected, seeing that the same factors are acting as in simple hyperventilation, but in the opposite way.

The fact that in several cases we find a fall in blood-pressure differs from the results of the experiments of several investigators on normal subjects, e.g., Raab, and thus it *might* be a reaction characteristic of epilepsy, but we have no control experiments on normal persons and are not able to express any opinion on this question.

It seems to us to be interesting that without exception the CO₂ experiments on patients with hysteria are accompanied by a rise in blood-pressure. This

might be correlated with a greater sensibility of the vasomotor centre towards CO_2 , or perhaps with the decreased alkali reserve of 'nervous' people and patients with neurasthenia, found by Laignel-Lavastine and by Cornelius and Vincent (cited by Guttmann). If the alkali reserve is decreased, a certain percentage of CO_2 in the air inhaled will set free a larger amount of CO_2 in the blood, and thus a stronger effect upon the central nervous system will be caused. If an epileptic makes a simple hyperventilation, during which his alkali reserve will be diminished, and he is then given CO_2 , a rise in blood-pressure will *always* take place; whereas, as we have shown, in several epileptics, who have not first made a simple hyperventilation, there is a fall in blood-pressure.

II. If we now analyse the changes in the composition of the blood, which are the consequence of the hyperventilation, we shall only mention the most important points—those which are of special interest to our series of investigations.

The hyperventilation is accompanied by a ventilation of CO_2 , and this causes an alkalosis, a non-compensated or partly compensated CO_2 deficit (van Slyke). At the same time a decrease of the alkali reserve gradually arises (Henderson and Haggard), which is caused, amongst other factors, by the secretion of a more alkaline urine. According to the equation of Henderson and

Hasselbach $\left(C_{\text{H}} = k_1 \frac{C_{\text{H}^2} \text{CO}_3}{C_{\text{BH}} \text{CO}_3} \right)$ the decrease in the amount of alkali reserve

at any rate means a partial compensation of the CO_2 ventilation; the $C_{\text{H}} +$ of the blood is displaced less in an alkaline direction than would be the case if the alkali reserve were constant. It is this alkalosis which forms the basis of the theory of the genesis of the fit provoked by hyperventilation, which is accepted by most investigators. Besides this, there is, however, a decrease in the amount of free O_2 in the peripheral vessels, and thus also in the tissues, due to the fact that oxygen is more firmly bound to hæmoglobin when CO_2 is inhaled—the so-called 'Bohr effect.'

On CO_2 inhalation, the same factors are acting, but in the opposite direction; an excess of CO_2 arises, i.e., an acidosis, which is partly compensated by the organism through an increase of the alkali reserve. On account of the increased amount of CO_2 in the vessels, more oxygen is freed from the hæmoglobin; at the same time the peripheral circulation is easier, and the tension of oxygen in the tissues is thus increased.

Different experimental investigations on animals (e.g. those of Wolff and Lennox) have shown that during hyperventilation there is a constriction of the vessels in the pia, during CO_2 inhalation a dilation of these vessels. These changes in the lumina of the vessels will have an effect, as far as the oxygen tension of the tissues is concerned, parallel to the changes in the composition of the blood mentioned.

O_2 inhalation produces conditions which mostly resemble those caused by simple hyperventilation, but the amount of oxygen physically absorbed in the

blood-plasma is larger and the CO_2 tension in the alveoli also and therefore in the blood as well—the resistance against respiration being greater through a mask, though it is not very much. This seems to agree with the fact that the results of the O_2 experiments mostly resemble those of simple hyperventilation, but the epileptic phenomena occur more seldom and are less pronounced. It is thus seen that on simple hyperventilation there is a decrease, on CO_2 hyperventilation an increase, of the oxygen tension of the tissues.

The importance of anoxæmia as the cause of the epileptic convulsions has often been discussed. Recently Foerster has attributed to it some importance. Through a pronounced anoxæmia it is possible in normal subjects to provoke convulsions which strongly resemble those of epileptics. It seems natural to us to reckon with the possibility that the occurrence of anoxæmia on simple hyperventilation, and its absence on CO_2 hyperventilation, may possibly play a part towards respectively causing or preventing the appearance of fits in these experiments. It must then be supposed that the brain of epileptics is more sensitive to lack of oxygen than that of normal individuals; in other words, their 'Krampfbereitschaft' might partly be due to this fact. As, however, a series of other changes take place—in the ion-contents, in stability of the colloids and through this in the permeability of the cells, etc., changes which we have not examined during our different experimental conditions—what we have said about anoxæmia can only be looked upon as one possibility out of many.

Lastly we will briefly discuss the single case in which CO_2 - O_2 hyperventilation caused a fit. It was that of a patient in whom a pronounced 'Krampfbereitschaft' must be supposed to be present, as in four out of five different experiments carried out on him he exhibited epileptic phenomena. During inhalation of 5 per cent. CO_2 - O_2 mixture he had an 'absence' by the third minute, at a time when he had quite emptied the accumulation bag, and we had not yet time to regulate the delivery. This result seems to argue against what we have said above about the importance of anoxæmia. But Jacobi has shown, in a series of fine microscopical examinations of the vessels of the pia during simple and CO_2 hyperventilation in dogs, that, while simple hyperventilation generally caused a constriction, and CO_2 hyperventilation a dilatation of the vessels, at the beginning of the CO_2 inhalation (especially when this gas is present in low concentration) a passing constriction of the vessels may occur, and at the same time there is a lower threshold for the electric release of a fit of convulsions. It seems natural to us to suppose that this is what has happened to our patient; in spite of a beginning acidosis he has had a passing constriction of his vessels and following this a decrease in the oxydisation of the tissues. On testing him with 10 per cent. CO_2 no epileptic phenomena were provoked.

If this explanation of the only divergence from the rest of the results is correct, it pleads more in favour of than against the importance of anoxæmia in the epileptic hyperventilation fit.

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