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Directeur de séance : **J. HANDELSMAN** de Varsovie

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Rapports présentés par :

U. CERLETTI de Rome.
R. DRESZER de Poznan.
A. M. FIAMBERTI de Varese.
J. J. LÓPEZ IBOR de Madrid.
L. J. MEDUNA de Chicago.
M. SAKEL de New-York.

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Clinical and biochemical indications of the convulsive and of the carbon dioxide treatments

by Dr. **L. J. MEDUNA**

Associate Professor, University of Illinois, Chicago, Illinois.

THE indication of the convulsive treatments in different varieties of depression seems to be established. The results have been so gratifying that, I believe, we may consider the convulsive treatment — the inducing of camphor-, metrazol-, picrotoxin-, and electric convulsions — the specific treatment of depressive states. With respect, however, to schizophrenia and different neurotic conditions, the authors disagree as to the usefulness of these biological therapies. From the inception of convulsive therapy, I contributed to this inconsistency by my inadvertence to follow up clues already available in 1937, the year of the publication of my monograph, " Die Konvulsions Therapie der Schizophrenia ".

A recapitulation of a few conclusions at which I had arrived and which I expressed even in that monograph will clarify the inconsistency of which I am speaking. In this monograph I offered the following conclusions :

" The schizophrenics cured by my method (convulsive treatments) must be considered pseudo-schizophrenics, i. e., persons suffering from a symptomatic schizophrenia, even if there is a direct heredity (of schizophrenia) in their families " (P. 112). And on page 113 of the same monograph : ,, My method offers not only a therapeutical possibility but also a differential diagnostic means. We must diagnose the disease of those patients who were cured by the method as symptomatic schizophrenia. The refractory cases suffer from endogeneous schizophrenia. "

The distinction between the two forms of schizophrenia may, in 1937, have appeared academic, with undue emphasis on the purely formal ; and yet it contained a core of intimated, though not recognized, importance. Seven years of research in collaborations with Drs F. J. GERTY, V. E. URSE, J. J. BRACELAND, and W. S. MCCULLOCH, and with J. A. VAICHULIS, Ph. D., approximated the answer to the riddle as to why some cases of schizophrenia were not amenable to the convulsive treatment. And the answer, strangely enough, could have been found in my monograph of 1937, or in the earlier works of REGIS, BARUK, and MEYER-GROSS. From my monograph, I quote from the 119th and following pages :

" As MEYER-GROSS stated, true amnesia is of greatest rarity in schizophrenia ; and yet, true amnesia I found quite frequently. One patient, for instance, who fell ill in Paris, France, and was transported from there to Budapest, Hungary, did not remember having left Paris, coming to Hungary, being admitted there to a state institution, or any symptom of his mental disease. Another patient laughed heartily when I repeated to him some of his bizarre statements and told him of some of his actions while he had been ill, statements and actions of which, apparently, he had no recollection... Quite frequently, there is disturbance of consciousness, a disturbance resembling a twilight-state... In many cases, it was impossible to diagnose these disturbances of consciousness while the disease persisted ; I recognized them only after the patients had recuperated and had recalled the experiences which they had had during their illness. One patient, for instance, told of a visual disturbance : he had seen everything as if through a veil. Everything had appeared to him as if he had been in a dream. This disturbance he did not conceive to have been hallucination for he had known that the dream-like quality of things was not real ; but he though that his vision had been disturbed because during his illness he had felt as if he were drunk. "

Today it is clear to everyone of you that these conditions which I considered those of " symptomatic schizophrenia " or " pseudo-schizophrenia " were but those of the " onirisme " of REGIS, or the " oneiroid state " of MEYER-GROSS. Such identification I did not make at that time ; and since that time I have

been able to make it only by a wide detour which has led me to detect some of the biochemical disturbances accompanying or probably causing the disturbance.

In 1942, a time when we still though in terms of " true " and " symptomatic " schizophrenia, Drs. GERTY, URSE, and I examined an unselected group of schizophrenics and found that of these so-called schizophrenics, about 60 per cent had

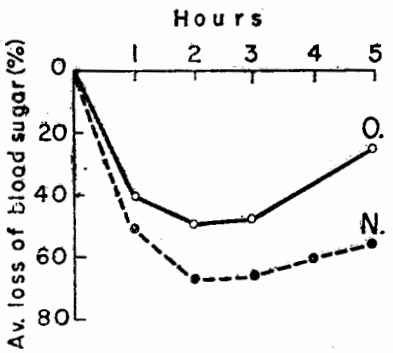

FIG. I. — Average loss of blood-sugar expressed in per cent of the fasting blood-sugar. N. represents the average loss of blood-sugar of twenty rabbits injected, intraperitoneally, with 20 cc. of freshly taken blood of normal persons ; and, one hour later, injected subcutaneously, with one unit of insulin per kg. per rabbit. O. represents the average loss of blood sugar of 34 rabbits injected, intraperitoneally, with 20 cc. of freshly taken blood of acute schizophrenic patients ; and, one hour later, with 1 unit of insulin per kg. per rabbit.

an anti-insulinic factor in their blood. We attributed the presence of this factor to a disturbance in the function of the anterior lobe of the pituitary body, which lobe produces a hormone with similar biological effects.

The presence of this anti-insulinic factor was demonstrated as follows : 20 cc. of freshly taken blood of normal persons was injected into each of a number of rabbits, intraperitoneally ; and one hour later I unit of insulin per kg. per rabbit was injected subcutaneously. Thirty minutes after the subcutaneous injection of insulin, and each hour thereafter until the fifth hour, the blood-sugar of the animals was determined. The comprehensive curve of 20 experiments showed distinctly that normal blood, given one hour before the insulin, did not protect the animals against the effect of insulin since the " normal

blood-insulin " blood-sugar curve proved to be the same as the simple insulin hypoglycemic curve. Similarly, schizophrenics' blood and insulin were injected into rabbits ; and it was found that the schizophrenics ' blood inhibited or lessened the effect of the insulin. *Thus it was demonstrated that the blood of some schizophrenic patients contains a factor which inhibits the effect of insulin.* This inhibition was manifested by the blood of 64 % of the patients (Fig. I). Hence, it was concluded that schizophrenia falls into two pathogenetically different subdivisions.

Fasting blood-sugar examinations showed, furthermore, that if there is a disturbance of the blood-sugar regulation in one group of so-called " schizophrenic " patients, it cannot be accounted for simply by an increase in an anti-insulinic factor because such increase would be accompanied by a uniform increase in the fasting blood-sugar values. Such uniform increase in the blood-sugar values does not, however, occur.

An explanation of this enigma I sought by considering the role of the adrenalin and that of the glycotropic hormone of the anterior pituitary body. This hormone I assumed to be identical with the anti-insulinic factor found in the blood of one group of so-called " schizophrenic " patients. According to my hypothesis, the increased anti-insulinic factor is a spurious compensation for a decreased function of the adrenalin gland.

In order to throw some light on the complexities of the problem, BRACELAND, VAICHULIS, and I introduced EXTON-ROSE's l-hour two-dose test in the hope that its use would enable us to divide the schizophrenics into easily differentiable groups. This test revealed that only 37 % of the so-called " schizophrenia " patients examined had a normal tolerance curve and that 48 % of these patients had showed an abnormal rise during the second half hour of the test (Fig. II). The only cogent interpretation of these abnormal curves is that the action of the insulin in these patients was delayed ; and " the evidence to date seems to indicate that the delay in the action of insulin in these patients can be attributed to the anti-insulinic factor already demonstrated in their blood ". These facts show that we had two sets of characteristics peculiar to one group of schizophrenic patients.

The next question to be decided was whether the group of schizophrenic patients possessing these two sets of characteristics was identical with my pseudo-schizophrenic group and with patients suffering from REGIS' and other authors' " onirisme " and from LANGFELDT'S " schizophreniform states ".

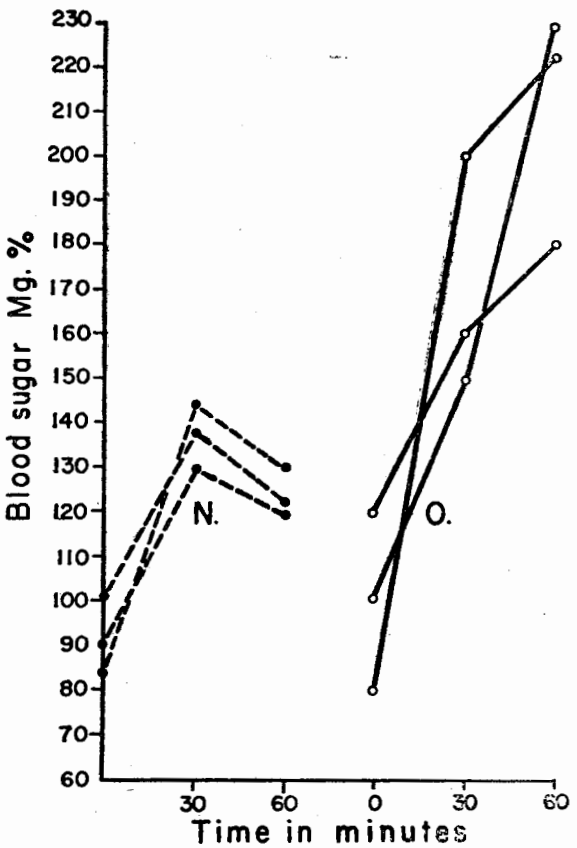

FIG. II. — Exton-Rose 1-hour two-dose glucose tolerance test. N. represents the blood sugar of three normal persons; O. represents the blood-sugar of three schizophrenic persons.

Finally, we agreed with LANGFELDT that these diseases " in reality have no connection with endogenic (classical) schizophrenia ". The most outstanding subjective feature of " pseudo-schizophrenia " is a disturbance of the sensorium, a disturbance which endows it with a dreamlike but nightmarish quality. This disturbance may range from a sensation of change in one's body and in one's environment, to a dreamlike condi-

tion, even to utter confusion. Hence, to give the disorder a name denoting its outstanding characteristic, I referred to it as " oneirophrenia ". This term is new only in form. Both the name and the condition which it identifies have been well known in the French literature from the beginning of the 20th century.

The term " oneiroid " or " onirisme " was introduced into the French psychiatry by REGIS in 1901. REGIS described the disturbance-the prototype of what I have called oneirophrenia — as a disturbance which in its psychiatric aspect corresponds to delirium tremens, typhoid delirium, and different toxic and fever deliriums of the English literature, and which overlaps many KRAEPELINIAN diagnoses. These disturbances of the sensorium are characterized by a disoriented, dreamlike state interspersed with visions of moving and terrifying objects. These same disturbances have been described, by BARUK, as those accompanying intracranial hypertension and tumors of the third ventricle and of the infundibulum, and, by ALAJOUANINE, as those accompanying narcolepsy.

As for the physiopathology of " onirisme ", the French psychiatrists have been inclined to ascribe it to disturbances of the basal ganglia. This theory is based mainly on cases of tumors of the infundibulum and of the third ventricle and, in some cases, on encephalitis, in which the patients have developed a similar condition. BARUK has emphasized that certain chemical substances, such as alcohol and peyotl, can produce " onirisme ". TRUBERT has described an "oniric" condition in connection with a colibacillus infection following an otherwise normal birth. A similar observation has been published by R. CORNU. The term " oneiroid " appeared in the German literature with MEYER-GROSS, who called it " oneiroid states " or " oneiroid experiences ". MEYER-GROSS described the illusionary, dreamlike condition in nine cases : three of these developed the condition as one superimposed upon schizophrenia ; three others suffered from it in conjunction with depressive diseases ; and, finally, three suffered from the pure form of the disturbance.

The fact that the oneiroid condition can appear in conjunction with many unrelated diseases such as tumors, encephalitis, schizophrenia, and manic-depressive disease should not prevent our recognizing that the syndrome itself can and does

appear independently and in the absence of any other mental or physical disorder. Therefore, instead of calling it *oneiroid* condition or *onirisme*, I have proposed this name for the condition : *oneirophrenia*. As a clinical definition of oneirophrenia, I offer the following : The name *oneirophrenia* indicates a syndrome which, in the overwhelming majority of cases, begins acutely or subacutely and is benign in the sense that it tends to spontaneous remission with complete restitution of the premorbid personality. It is characterized by a specific alteration of the proprio and exteroperceptions which alienates the afflicted individual from his environment.

The altered relation to the environment is caused by changes in the field of perception, not by parasymbolic interpretation of normal perceptions, and is referred to by the patient as changes in his own body, or in the outer world, or in both, according to the relative participation of the proprio- or heteroceptors in the process. The degree of the pathologic change in the sensorium ranges from experiencing a change in one's sense organs or in one's body, to living in an enormous, terrifying nightmare, an experience which cannot be compared or linked to anything hitherto encountered.

Changes, of all degrees of severity, in the patient's orientation are typical of the disease ; so a disturbance of the somatopsychic or of the allopsychic orientation, or of both, is a basic, fundamental symptom of the disorder.

Disturbances of memory are always limited to the duration of the condition. Paramnesia during the disease and retrograde amnesia after the disease are common.

Disturbances in the thought process are contentual or thematic and leave intact the intrinsic properties of thinking, i. e., the formal and the symbolic logic. The lack of disturbance of the formal and the symbolic logic, in these cases, I have ascertained by using the VIGOTSKY test. All of the tested patients who suffered from true schizophrenia manifested, in the VIGOTSKY test, a disturbance in categorical and symbolical thinking, while all the pure oneirophrenic cases showed that the intrinsic properties of their thinking were intact.

A highly significant feature of oneirophrenia is the lack, on the part of the patient, of any primary delusion.

Emotional expressions of the oneirophrenic patient do not deteriorate as they do in the schizophrenic patient ; furthermore, the emotions themselves are qualititavely appropriate — although possibly not to reality — to the unreal experiences of the patient.

In no case do we see a disintegration of the highest psychological functions : the patient never loses the unity of his personality, never becomes demented.

Common to all cases of oneirophrenia is a disorder of the regulation of the blood-sugar level under stress (tests). If we knew the factors producing this disturbance, including their mode or modes of action, we could attempt a subdivision of oneirophrenia on an etiological basis. Until further research enables us to do so, it is useful to recognize two distinct clinical froms of oneirophrenia. These froms express only gradations of the process.

1. Simple oneirophrenia. This form may develop under either of two different prerequisites : one, if the alterations in the central representations or mediators of the proprioceptors are greater than those of the exteroceptors ; two, if the affliction is such that it still permits the patient to recognize the pathological nature of the process even though the central representations on mediators of the exteroceptors are more affected than are those of the proprioceptors. In the latter case, the patient does not project his disturbance upon the outside world ; that is, though the patient experiences a change in the outside world, he recongnizes that not the world, but he, has changed. This form of oneirophrenia — that is, simple oneirophrenia — is seldom complicated by hallucinations.

2. Deliroid oneirophrenia. In this form, the central representations or mediators of the exteroceptors are affected to such a degree that the patient's sensorium has become clouded. This cloudyness of the sensorium ranges from a hazy indistinctness, to the obscurity of delirium. The condition is complicated, as a rule, by the presence of hallucinations. The patient projects his troubles upon the outside world which he experiences as a dream, a staged artifice, or as a fantastic, terrifying nightmare.

In the following paragraphs I shall describe the biochemical changes concommitant to oneirophrenia.

These changes can be summarized and described as a disturbance of the blood-sugar level regulation. This disturbance is characterized by the following features : (1) a sustained blood-sugar curve in the intravenous glucose-tolerance test ; (2) a positive diabetic-like blood-sugar curve in the EXTON-

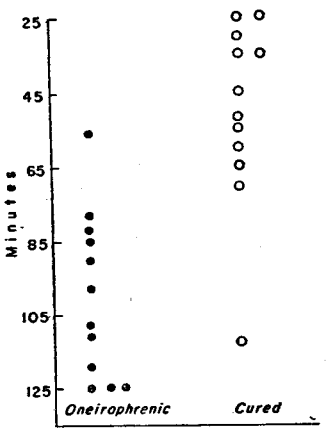

FIG. III. — The time when the blood-sugar returns to the original fasting value after intravenous glucose tolerance test. The black dots represent the returning time of 12 oneirophrenic patients while ill ; the white circles represent the returning time of the same patients after they had been cured.

ROSE test ; (3) resistance to insulin in the intravenous insulin-tolerance test ; and (4) increased anti-insulin factor in the blood and in the urine. In using the intravenous glucose-tolerance test, I found that, in the normal control group, the time which elapsed for the return of the blood-sugar to the original fasting values varied from 50 to 70 minutes. On the other hand, in using the intravenous glucose-tolerance test, I found that, for oneirophrenic patients, the average length of time necessary for the blood-sugar to return to the fasting value was 100 minutes ($\sigma = 5.7$).

This almost doubled " returning time " of the blood-sugar value is not only statistically significant but, also, pathologically characteristic. At random I took, for testing, twelve oneirophrenic patients. These patients, while oneirophrenic, had an average " returning time " to the base line of 110 minutes

(σ = 5.7.) ; after recovery, they had an average " returning time " of 52 minutes (σ = 8.7). The probalility that this change was due to chance is, by using R. A. FISCHERST, infinitesimally low (Fig. III).

These blood-sugar-tolerance curves lie somewhere between these of normals and those of diabetics; furthermore, the behavior of the blood-sugar during the test parallels the psychiatric picture inasmuch as when the oneirophrenic condition is cured, the sustained bood-sugar curve returns to the value of the blood-sugar curve of normals.

The EXTON-ROSE test is a glucose-tolerance test based on the fact that the response to successive doses of glucose in normals is different from that in diabetics. In a normal individual, the first dose of sugar produces an elevation in blood sugar. If a second dose of sugar is given 30 minutes after the first dose has been given, there is a very slight rise, or even a slight fall, in the blood-sugar. On the other hand, the diabetic responds to a second dose of sugar by a further increase in the blood-sugar concentration.

In the EXTON-ROSE test, all the oneirophrenic patients display a positive, diabetic-like blood-sugar. The diabetic curve appears with the psychiatric disturbance and, in an overwhelming majority of cases, disappears when the sensorium of the patient clears up.

The insulin-tolerance test is made by giving an intravenous injection of 0.1 unit of insulin par kilogram of body weight. In normals, the average loss of blood sugar during the insulin-tolerance test, at the deepest point of the curve, is 57.5 % of the fasting blood-sugar value.

The insulin-tolerance test revealed the average loss of blood-sugar by oneirophrenic patients to be 36 % of the original fasting blood-sugar. The standard deviations of the two sets of values are 7.9 % for the normals, and 7.7 % for the oneirophrenics. The probability that the difference between the two sets of values is due to chance is statistically negligible.

Oneirophrenic patients' resistance to unsilin is a reversible phenomenon which — as does the sustained blood-sugar in the glucose-tolerance test — disappears after the patient has been cured.

From the presence of an anti-insulinic factor in the blood of the oneirophrenic patients, I postulated the presence of a hyperglycemic factor in the urine of these patients. The soundness of this postulate Dr. VAICHULIS and I sought to determine. We found that if we precipitated the factor in question from the urine of normals and injected it into white rabbits, it increased the blood-sugar of these rabbits by 37 % of the fasting value ;

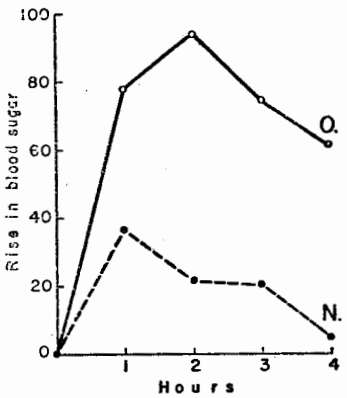

FIG. IV. — Average blood-sugar curve of rabbits injected, intraperitoneally, with anti-insulinic factor prepared from urine. N. represents the average curve of 21 rabbits, each injected, intraperitoneally, with anti-insulinic factor precipitated from 24 hours' urine specimen of 21 normal individuals. O. represents the average blood-sugar curve of 34 rabbits injected, intraperitoneally, witch anti-insulinic factor precipitated from 24 hours' urine specimen of 34 oneirophrenic patients.

that one hour after the injection it had a standard deviation of 27.5 % ; and that four hours after the injection the blood-sugar curve had dropped and returned to normal or to almost normal. The hyperglycemic factor secreted during the same period by our oneirophrenic patients produced more than twice the increase in the blood-sugar of the rabbits. In these patients, one hour after the injection the increase in the blood sugar was 78 % above the fasting blood-sugar level ; two hours after the injection, the blood-sugar level had risen to 94 % above the fasting level ; and four hours after the injection, the blood-sugar level was still + 61 % above the fasting level. Thus, oneirophrenics as a group are distinguishable by an increased urinary excretion of a hyperglycemic factor (Fig. IV).

A very interesting and, I believe, a significant phenomenon

is that all these biochemical disturbances parallel the disease and disappear after the disease has cleared up. To illustrate this statement, I present three average curves of the behavior of the blood-sugar during the insulin-tolerance test : the standard normal curve ; the curve of 31 oneirophrenic patients while they were sick ; and, finally, the curve of the same patients after they had been cured (Fig. V).

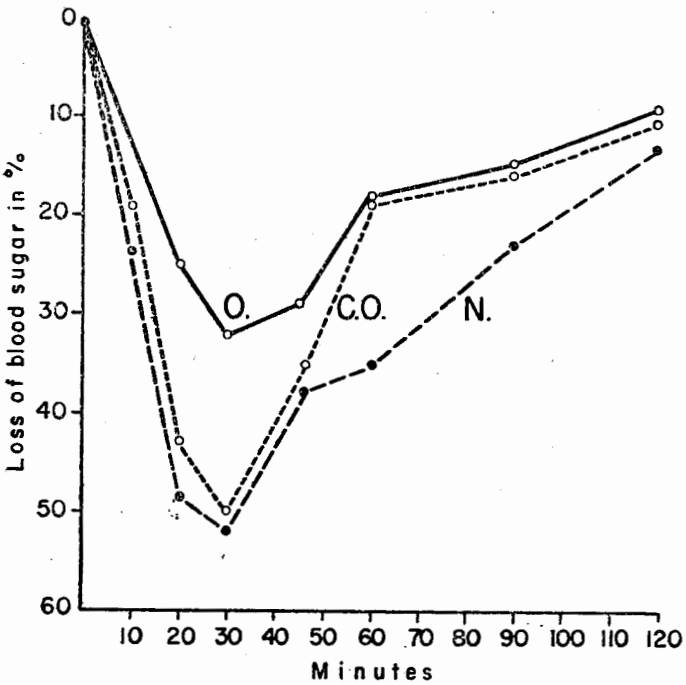

FIG. V. — Intravenous insulin tolerance test. One-tenth of a unit of insulin was injected, intravenously, and the blood-sugar determined at intravals during a two-hour period. The blood-sugar values are expressed in per cent of the original fasting values. N. represents the standard normal blood-sugar curve; O. represents the average blood-sugar curve of 31 oneirophrenic patients while they were ill ; C. O. represents the average blood-sugar curve of the same patients after they had been cured.

Summing up our biochemical considerations, we can state that oneirophrenic patients are characterized by inefficiency in handling a sudden increment in the concentration of blood-sugar and by resistance to intravenous insulin. The two phenomena seem to explain each other, inasmuch as a patient who is resistant to insulin is bound to be inefficient in handling the glucose in his blood. The question arises as to what could be the

possible explanation of these patients' resistance to insulin. I believe that I found the answer in demonstrating the presence of an increased amount of hyperglycemic factor in the urine of these patients. This factor increases the blood sugar of the experimental animals. Although I am unable to identify this factor, some considerations have led me to believe that this factor is either identical with the so-called diabetogenic factor of the pituitary body or with a derivative of it. My assumption gains support from the work of PRICE and CORI. According to these investigators, one of the anterior pituitary factors has the following important role in the metabolism of the carbohydrates : it inactivates the enzyme hexokinase and thus prevents the first phosphorilation of glucose to glucose-6-phosphate. This action of the factor is prevented by insulin which, therefore, is a true antagonist of the pituitary hormone. The anti-insulinic factor which I found in the urine of oneirophrenic patients acts, in Warburg apparatus, similarly.

Thus, I postulate a psychiatric condition based on a partial inactivation of hexokinase, a partial inactivation due to overactivity of the anterior pituitary hormone. This inactivation, in turn, inhibits the phosphorylation of glucose, the source of nervous energy. Some systems, especially those serving the integration of perceptions — i. e., the sensorium — may be more sensitive to this exigency than others ; or a competition may arise between them and other systems, in which competition the more sensitive nervous systems break down.

We should not think, however, that the oneirophrenic disturbances may develop only through inhibition of the hexokinase. I have seen oneirophrenic conditions develop under the effect of barbiturates. Now, as QUASTEL has shown, barbiturates inhibit the action of a flavoprotein.

Identical clinical pictures develop in about 1 % of all the cases treated with sulphadiazine or sulphanilamide. The sulpha drugs are known to be inhibitors of various enzymes of the carbohydrate metabolism. So sulphanilamide has been reported to inhibit carbonic andrydrase and catalase. Alcohol delirium, i. e., delirious oneirophrenia, develops if the intoxication has inactivated cytochrome oxidase and, probably, other enzymes.

Oneirophrenic conditions seem, therefore, to develop whenever

enzymes of the carbohydrate metabolism are inhibited or attenuated. This inhibition may be produced, I have concluded, (1) by a disturbance in the quantitative relation of hormones affecting the carbohydrate metabolism, and (2) by any compound directly poisoning the respective enzymes.

The carbohydrate metabolism can be disturbed not only in its intrinsic mechanism, but also by lack of glucose or of oxygen. Accordingly, psychiatrically identical states will develop in hypoglycemia or in hypoxemias of any kind. The disturbances of the sensorium — fogging and " confusional states " — are well known in spontaneous and artificial hypoglycemias ; and well known is the illusionary psychotic-like condition of high altitude fliers with inadequate masks for oxygen.

The so-called " confusional states " — i. e., oneirophrenias, according to the clinical description of these states — following carbon monoxide, aniline, sulphanilamide, and sulphapyridine poisoning are essentially anoxemic conditions resulting from conversion of hemoglobin into compounds such as methemoglobin or sulphemoglobin, compounds which prevent the formation of oxyhemoglobin and which thus produce anemic anoxia. These different causes have different modes of action, but they all converge in the same direction, i. e., towards the metabolism of the carbohydrates ; if a disturbance has been set up in the metabolism of the carbohydrates, disturbance has been set up in the metabolism of the carbohydrates, oneirophrenia ensues.

Through evaluating the clinical evidences and the results of the biochemical tests, I believe that I am now able to define the disease group in which — in addition to the depressions — the convulsive treatment is to be used with good results. The group in question is the oneirophrenic group, a group characterized clinically by a disturbance of sensorium and biochemically in the ways which I have described.

The mode of action of the convulsive treatments in these diseases is that of a decrease in the pituitary function or an increase in the adrenal function. There seems to be some indication that the increment in the adrenal function is a pertinent factor during the convulsive treatments and that the decrease in the pituitary function is secondary to the change in the

adrenal function. If such indication can be substantiated, we have the explanation of the overall failure of shock treatments in most of the psychoneurotic conditions. These conditions, apparently, are caused not by a failure of any gland, although many exceptions are permissible to this rule, but by a failure of some other mechanism.

The nature of this mechanism is unknown ; nevertheless, I shall present a hypothesis of it, which hypothesis is based on some common biochemical properties of the chemical agents which have been used successfully in the treatment of psychoneurotic conditions. These chemical agents are different barbiturates, nitrous oxide, ether, and carbon dioxide.

KLAESI, in 1921, introduced the use of barbiturates in such form as to produce continuous, prolonged narcosis for purposes of treatment in psychosis. BLECKWENN, in 1930, introduced the intravenous use of sodium isoanylethylbarbiturate for exploratory purposes, mainly in the catatonic, but also in other forms, of schizophrenia.

HORSLEY, in 1936, published the barbiturate technique to obtain information of diagnostic value and to utilize cathartic phenomena rendered more bearable to the patient by the produced half-sleep or twilight state. Harold PALMER, however, noticed that, besides this psychological facet of abreaction, some other, biochemical, forces must be at work during the intravenous barbiturate treatment. That he did so is clearly seen in such remarks of his as these : " In simple tension syndromes..... the session should be continued for not less than halfhour for I do not believe that, in this class of cases, narco-analysis strictly considered will of itself materially effect the patient's cure " ; and, further : " It is important to bear in mind — since there is no satisfactory theory of mind which would meet with universal acceptance of psychiatrists — that the facile use of such terms as " dissociation ", " removal of inhibition ", and the like, may correspond to nothing more than useful and, indeed, indispensable psychiatric hypotheses. Similarly, it is only speculation which can serve to explain the precise pharmacological processes involved in these techniques. Nevertheless, it is tempting to suppose that under the influence of the narcotic the patient's mental condition is less influenced by more recently developed psycho-

logical constructions, thereby allowing the mind to work in a more physiological manner ".

ROGERSON, in 1944, introduced nitrous oxide as a specific method of dealing with resistance as this term is understood by the FREUDIAN psychoanalysts.

PALMER, who, in 1944, introduced ether " as a method of recovering amnestic material and of inducing abreaction ", seems to be in doubt as to whether the usual psychological features — besides being the most obvious ones — are the most essential factors of the technique, when he writes : " One can only speculate concerning the essential effective component parts of the technique, and there are many points to consider, the most obvious being the emotional catharsis and the reintegration in consciousness of the previously forgotten material ".

The purely psychological features of these treatments are so preponderate that, in spite of PALMER's slight warnings, one can not help considering them the main responsible factors of the recovery and neglecting the more basic physiological implications. Preponderance — or, even, appreciable presence — of psychological factors do not, however, characterize the carbon dioxide therapy, an account of my development of which I first published in 1947. This treatment has the unique feature of attacking directly some neurotic symptoms in spite of my intentional omission of any suggestion and my avoidance of catharsis and of symbolical approach to the psychoneurotic symptom. Recovery thus depends upon only the effect of the gas upon the brain tissue of the patient.

This carbon dioxide treatment consists of inducing anaesthesia through repeated inhalations of a gas mixture of 30 % carbon dioxide and 70 % oxygen. During the administration of the gas the patient is lying on a bed or on a comfortably padded treatment table. One nurse is necessary to handle the patient during the treatment. The same nurse counts the number of respirations taken by the patient ; she does so loudly in order that the patient can hear and can remember the last count that he has heard before the full anaesthesia has been achieved.

At the first treatment, it is advisable to give not more than 20 to 25 respirations. The patient is usually able to remember 8 to 16, sometimes even 20, respirations. If he does not lose con-

sciousness with about 25 respirations, an increase of 3 to 5 respirations should be made on the next day. Further increase in the number of respirations should be determined by the patient's reaction to the gas during the administration and afterward, on that or on the following day.

The 30 % carbon dioxide produces a remarkable alteration of almost every nervous activity. It may produce simple rudimentary sensory phenomena ; or complicated dreams, with or without emotional discharge ; or emotional discharge without any dream whatsoever ; or complicated conditions of temporary confusion, hypnagogic hallucinations, and intricate cortical and subcortical motor discharges.

After the patient has inhaled the gas, his respiration becomes somewhat increased and forced, his pulse rate and blood pressure increase, and flushing and perspiration may appear. Some patients lose consciousness at the third or fourth respiration ; some do not lose it in 15 to 20 or more respirations. Between the tenth and the fortieth respirations, indications of psychomotor excitement may be seen. The psychomotor excitement can take almost any form, such as a struggle to escape discomfort or, in some cases, a repetition of some struggle the patient has gone through in his life.

During the first 10 to 40 respirations, the lower extremities are flexed at the hip and knee joints and slightly abducted. (This position, in some cases, may be of sexual context.) There is also a slight flexor hypertonus in the upper extremities and, frequently, carpal spasm of both hands.

If the administration of carbon dioxide is continued beyond this phase — let us say to between 30 and 50 respirations — adversive seizures, lasting a few seconds, may appear. During these seizures the pupils react to light. The movements of the patient during this phase resemble bicycling ; sometimes they imitate quadrupedal locomotion. At 50 to 60 inhalations, plantar responses disappear, and sometimes BABINSKI's sign can be elicited. If, in some cases, the treatment has been prolonged beyond this phase to the next stage, say from 60 to 90 or more respirations, the pupils become rigid, and decerebrate rigidity develops.

The sensory phenomena are mostly optical in nature and con-

sist of the appearance of a vague reddish light or small spots in the visual field. These spots, or points, or dots arrange themselves into geometrical patterns or, quite often, into elaborate figures with a straightforward or gyrating movement ; or they may develop a perspective and become an actual dream. These dreams, in some cases, appear to be open to symbolic interpretation. In some other cases, they are so weird and fantastic that they may defy any description ; or the patient may become the subject of an ecstatic condition such as that of some epileptic auras or of some religious experiences.

During this whole procedure the patient is free from any danger. Although I have administered more than 20,000 carbon dioxide treatments, I have seen no complications other than one tongue biting and three or four spontaneous urinations. It must be understood, however, that before the patient is submitted to the carbon dioxide treatment a thorough physical examination should be made, one which includes the tracing of an electrocardiogram.

There is no set rule to determine the duration of the treatment. I usually give the treatment three times a week. Each treatment takes about six minutes : about two minutes before the administering of the gas, during which time I orient myself by asking the patient whether he has felt any kind of change since the previous treatment ; about 30 to 120 seconds for the administering of the gas ; and two or three minutes in which I question the patient regarding the experiences which he has had during his inhalations of the gas.

The patient can leave the hospital or the office immediately after the treatment. The number of treatments necessary to achieve improvement in my group have varied from 20 to 150. If the patient does not experience considerable improvement during the first 20 or 30 treatments, there is little hope, I have found, that further treatment will be of any help to him. In many cases it is necessary to experiment with various depths of anaesthesia in order to determine the dosage of gas therapeutically most useful for the individual patient. I usually experiment in the following way : On the first occasion, I administer the gas, giving the patient 25 respirations. On the next day, I question the patient as to any change in his condition. Two or three times

on consecutive days, I repeat the treatment, with the same number of respirations. Then, if there is still no change, I increase the number of respirations to 30. After repeating the procedure a number of times — in any case, in about 10 to 15 treatments — I am able to establish the necessary degree of saturation with carbon dioxide.

This treatment is ineffective in the anankastic reactions, such as the obsessive and compulsive neuroses and the classic form of hypochondria. And — as has been established by LOEVENHART, LORENS, and WATERS, who have studied the effect of carbon dioxide on psychotic patients — this treatment is of no permanent help in any psychosis. On the other hand, carbon dioxide inhalations make easily manageable a great percentage of patients with conversion symptoms, such as those patients who, without underlying organic pathology, create physical symptoms. Also susceptible to this treatment are two other groups of patients : those with faulty control of emergency reactions, such as anxiety neuroses with symptoms of sense of guilt or of inadequacy and irritability, and those with personality maladjustments manifested by social and unconventional behavior and by emotional instability.

Of a group of 100 psychoneurotic patients with such personality maladjustments, 68 showed a degree of improvement that can be considered practical cures. Comprising this group were patients with such varied neuroses as anxiety neuroses, spastic colitis, cardiac neuroses, female frigidity, male impotence, stuttering (35 cases), character neuroses (many cases), feelings of inferiority, homosexuality (a few cases), and other more vaguely defined neurotic conditions.

The diversity of these psychoneurotic conditions helped by the carbon dioxide treatment, and the similar variety of cases influenced by an entirely different psychiatric technique — a technique utilizing ether narcosis — preclude our assuming any one of the fashionable psychodynamic explanations and force us to speculate about the common features of the pharmacological processes involved in these different techniques and different chemical agents. Our speculation, fortunately, is based on facts — facts ascertained from experimentation — at least with respect to carbon dioxide and ether ; and we have every reason

to believe that nitrous oxide and barbiturates work in a manner similar to that in which the two other gases work — although, perhaps, by different chemical mechanisms.

What are the known actions of carbon dioxide upon the nervous cell, and how are they related to those of ether ?

Carbon dioxide, we know, produces the following effects on the nerve cells : (1) it increases the membrane potential of the nerve, which increase in the membrane potential is accompanied by a rise of the threshold of stimulation of the nerve ; (2) it increases the height of the action-potential and prolongs its duration ; (3) it increases the height and the duration of the negative after-potential ; and (4) it decreases the fatigability of the nerve cell. Carbon dioxide, we know, increases the ability of the nerve to conduct trains of impulses, because the presence of carbon dioxide delays the appearance of the signs of fatigue.

Some of these effects must be reproducible by administration of ether ; LORENTE de No, indeed, found them to be so. " In general it can be said that all the changes that ether induces in the nerve fibers are a consequence of the changes in the resting membrane potential..... If consideration is given to the effect of ether upon the membrane potential of the nerve it becomes clear that the changes in the electrotonic potential and in the threshold of stimulation are in the main a consequence of the changes in the membrane potential. *Ether begins its action by increasing the membrane potential* ".

It is understood that an increase in membrane potential — regardless of the means by which we have achieved it — implies an increased threshold of stimulation with respect to stimuli from both within and without the system thus changed. Of what kind, then, must be the structural organisation of any psychoneurotic syndrome that can be influenced by increasing the threshold of stimulation of nerve cells or of nervous circuits involved in the process ?

A tentative answer to this important question can be given if we conceive our nervous system as one having an inherent tendency to restore its previous balance or to achieve a new balance after the stimulus which has upset it has ceased. This function of the brain belongs to the order of phenomena we call homeostasis. Homeostasis within the nervous system can be achieved by

mobilizing various organizations. It can be achieved by mobilizing suppressive areas, which areas, by negative feed-back circuits, decrease or inhibit the function of pertinent cortical areas even if the nociferous stimuli persist. The components of these feed-back mechanisms are fairly well known ; for instance, area 4s, a typical suppressor area, receives its stimulation from cortico-cortical fibers of areas 4 and 6 ; the stimulation of area 4s is being transmitted through the nucleus caudatus to the brain stem ; the ascending pathway from the brain stem reaches the cortex again through the non-specific thalamic nuclei.

Homeostasis can be achieved also by the spreading of the stimulus through many relays to the appropriate motor cortex where adequate action is being initiated in order to arrest the stimulus and thus to allay the reverberation of the positive feed-back circuits. The components of this organization are, of necessity, complicated. They consist of afferent pathways to one or several sensory areas, of corto-cortical pathways from the sensory areas to the ideo-motor cortex, of the thalamic-hypothalamic-thalamic-cortical loops of each of the sensory areas, and, finally, of the cortico-cortical pathways to the motor-cortex, with its loops through the striatum and probably to the paraqueductal grey matter and back to the motor cortex where, finally, the proper action is initiated.

Homeostasis can be achieved, furthermore, by mobilization of similar or identical organizations through their removing the organism as a whole from the orbit of the nociferous stimulus if the stimulus itself, for some reason, can not be arrested.

It is easy to see that successful homeostasis, which is tantamount to successful living, is a matter of normally functioning negative and positive feed-back circuits. If the threshold of stimulation in any of these circuits is delayed by as little as a few milliseconds, homeostasis can not be achieved, and a continuous reverberation ensues within the afflicted circuits. The continuance of this self-regenerating function, if it lasts sufficiently long, synchronizes neighboring circuits into its orbits ; and when the output signals of these have spread to non-specific effectors, perverse, wayward, interminable reactions, i. e., psychoneurosis, is produced.

Which of the non-specific effectors will be drawn, by syn-

chronization, into the orbit of the primarily reverberating circuits depends upon the threshold values and, thus, upon the resistance of the respective effector system ; finally, this resistance, and not the original noxa, is responsible for the symptoms of the psychoneuroses. If the threshold of stimulation of the non-specific ideational system is the lower, an ideomotor neurosis will develop ; if the motor system is the weaker, a psychomotor neurosis will develop ; if the autonomic nervous system is the most irritable, a psychosomatic or an anxiety neurosis will ensue. Thus, obsessions and phobias are symptoms of ideo-motor neurosis ; stuttering, tics, nailbiting, compulsive actions, and grand hysteria are symptoms of the psychomotor neurosis ; spastic colitis, ulcers, and spasms are symptoms of the parasympathetic or somatic neurosis ; and, finally, anxiety is the classic symptom of the sympathetic neurosis. The illness will commence whenever the threshold of stimulation in the reverberating loops is lowered. A psychoneurotic condition is, therefore, a disturbance of the nervous net, a disturbance consisting of excessive prolongation of normal function and inducing originally non-affected nervous loops into a synchronous, pathologically prolonged function. Thus, the existence of a psychoneurosis can be explained by an abnormally low threshold of stimulation with respect to normal stimuli, or by a relatively low threshold of stimulation with respect to stimuli of exceptional strength. In either case, the logical biological treatment consists of raising the threshold of stimulation to the normal level of resistance to nociferous stimuli from within or from without.

This postulate seems to be fulfilled by the judiciously repeated administration of carbon dioxide and, to some extent, by that of the other gases.

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RESUMEN

INDICACIONES CLINICAS Y BIOQUIMICAS DE LOS TRATAMIENTOS CONVULSIVO Y POR EL ANHIDRIDO CARBONICO (1)

por L. J. MEDUNA

La convulsoterapia puede ser considerada actualmente como el tratamiento específico de la depresión. Pero no hay acuerdo respecto a su utilidad en la esquizofrenia y en diferentes neurosis. El autor recapitula sobre algunas conclusiones a las que llegó en su publicación " Die Konvulsions Therapie der Schizophrenie " en 1937. Afirmaba que las esquizofrenias curadas con su método debían ser consideradas como seudoesquizofrenias, es decir, personas afectas de esquizofrenia sintomática, aún en el caso de que hubiera una herencia directa (de esquizofrenia) en sus familiares. Las casos refractarios serían esquizofrenias endógenas. Hoy en dia ha identificado los casos de esquizofrenia sintomática o seudoesquizofrenia con el " onirismo " de REGIS o con el " estado oneiroide " de MEYER-GROSS. Ha llegado a esta conclusión debido a sus estudios bioquímicos.

Demostró que la sangre de algunos esquizofrénicos contenía un factor

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(1) Este resumen del informe del Autor ha sido hecho por el Dr MORALES BELDA.

que inhibía la acción de la insulina y supuso que era idéntico a la hormona glicotrópica del lóbulo anterior de la hipófisis. El aumento de dicho factor sería una compensación a una disminución de la secreción de adrenalina. Estos enfermos con estas características ¿ eran los mismos que él consideraba como seudoesquizofrénicos y luego como síndromes oneiroides ?

Analiza el concepto de onirismo. Propone el nombre de " oneirofrenia " para aquellos casos en los que el síndrome aparece independientemente y en ausencia de cualquier otro trastorno mental o físico. Serían características del onirismo :

(1) en la prueba de tolerancia a la glucosa intravenosa, una curva de glucemia prolongada ;
(2) en la prueba de EXTON-ROSE (dosis sucesivas de glucosa), una curva de glucemia de tipo diabético ;
(3) en la de la insulina intravenosa, resistencia a la hipoglucemia ;
(4) el factor antiinsulínico aumentado en la sangre y en la orina.

Todos estos trastornos bioquímicos ocurren paralelamente al síndrome mental y desaparecen cuendo este cesa. El síndrome oneiroide se caracterizaría por lo tanto por la imposibilidad de compensar un aumento súbito de la glucemia y por la resistencia a la insulina intravenosa. Basandose en investigaciones de PRICE y CORI, supone el autor, que el factor antiinsulínico actúa inactivando la hexokinasa e impidiendo así la fosforilización de la glucosa. De esta manera disminuiría la fuente de la energía nerviosa. Algunos sistemas cerebrales, más sensibles que otros, como los que realizan la integración de las percepciones, sucumbirían con más facilidad. El síndrome oneiroide se presentaría siempre que el metabolismo hidrocarbonado estuviese alterado, o bien porque las enzimas estuviesen inhibidas (barbitúricos, sulfamidas y sulfadiazina, delirio alcoholico) o porque faltase la glucosa o el oxígeno (hipoglucemia, vuelo de altura, alteraciones de la hemoglobina).

La convulsoterapia actuaría en el síndrome oneiroide disminuyendo la secreción hipofisaria y aumentando la función adrenal. Aquella disminución sería secundaria a este aumento.

La convulsoterapia fracasa en las psiconeurosis porque en estas la patogenia es distinta.

El autor hace un intento de explicación del mecanismo de las psiconeurosis. Se basa en la acción terapéutica de distintos productos farmacológicos (barbitúricos, monóxido de nitrógeno, eter, anhidrido carbónico). Con algunos de ellos la curación se realiza por un proceso psicológico de catarsis fundamentalmente, aunque deba pensarse que el fármaco contribuye tambien bioquímicamente de un modo todavía poco conocido. Con el anhidrido carbónico, lo fundamental es la acción del gas en el cerebro.

Describe el autor detalladamente la técnica de la administración del anhidrido carbónico y las reacciones que presenta el enfermo. El tratamiento es inocuo. Se administra una mezcla de un 30 % de anhidrido carbonico y 70 % de oxígeno, durante 30 a 120 segundos, tres veces por semana hasta un total de 20 a 150 sesiones. Está indicado en los enfermos con sintomas de conversión, neurosis de ansiedad con sensación de

culpabilidad o con inadaptacion e irritabilidad, y en personalidades mal adaptadas que se manifiestan por una conducta social anormal e inestabilidad emocional. Los efectos del eter son en todo semejantes.

El modo de acción curativo de estos fármacos es común a todos ellos, aunque el mecanismo químico presente diferencias. En las neuronas aumentan el potencial de membrana, aumentan el umbral de excitación, elevan y hacen más duraderos el potencial de acción y el postpotencial negativo y disminuyen la fatigabilidad del nervio. El efecto esencial es el aumento del umbral de excitación. El autor se pregunta : ¿ Que organizacion estructural tiene el sindrome psiconeurotico para que tal aumento del umbral actúe de modo curativo ? El autor basa su hipotesis en la función homeostática cerebral representada por la tendencia a restaurar el equilibrio funcional mediante la puesta en marcha de circuitos supresores o mediante la activación de zonas motoras que alejen al sujeto del estímulo. Suponiendo que en las psiconeurosis estuviera disminuido el umbral de estimulación, la homeostasis no se conseguiría y quedaría una repercusion continua en los circuitos supresores. " La continuación de esta función de autorregeneración, si dura lo bastante, sincroniza a los circuitos vecinos dentro de su órbita ; y cuando los estímulos se han extendido a efectores no específicos, se producen reacciones anormales, caprichosas, interminables, es decir, una psiconeurosis ". Aparecera un sintoma u otro segun cual sea el sistema menos resistente en cada individuo.

RÉSUMÉ

INDICATIONS CLINIQUES ET BIOCHIMIQUES DES CONVULSIVOTHÉRAPIES ET DES THÉRAPEUTIQUES PAR L'ANHYDRIDE CARBONIQUE (1)

par L. J. MEDUNA

La convulsivothérapie est considérée actuellement comme le traitement spécifique de la dépression. On n'est pas d'accord, au sujet de son utilité dans le traitement de la schizophrénie et des différentes névroses. L'auteur reconsidère quelques-unes des conclusions exprimées dans sa publication « *Die Konvulsions Therapie der Schizophrenie* » en 1937. Il y affirmait que les schizophrènes guéris par sa méthode devaient être considérés comme des pseudo-schizophrènes, c'est-à-dire comme des sujets atteints de schizophrénie symptomatique, même lorsque l'on observait une hérédité directe de schizophrénie dans la famille. Dans les

(1) Résumé et traduction par le Dr MORALES BELDA.

cas réfractaires au traitement, on aurait à faire à une schizophrénie endogène. Aujourd'hui, l'auteur est prêt à considérer comme identiques les cas de schizophrénie symptomatique, la pseudoschizophrénie avec onirisme de RÉGIS et l' « état oneiroïde » de MAYER-GROSS. Il arrive à cette conclusion grâce à ses recherches biochimiques.

Ces recherches démontrent que le sang de certains malades schizophrènes contient un élément, inhibant l'action de l'insuline, et identifiable à l'hormone glycotrope du lobe antérieur de l'hypophyse. L'augmentation du taux de cet élément compenserait une diminution de la sécrétion d'adrénaline. L'auteur s'est demandé si ces malades n'étaient ceux qu'il avait considérés comme pseudo-schizophrènes.

Examinant le concept d'onirisme, l'auteur propose le terme d' « oneirophrénie » pour ces syndromes particuliers avec absence de tout autre trouble mental ou physique. L'oneirophrénie se caractérise, pour l'auteur, par :

1° une courbe de glycémie prolongée à l'épreuve de tolérance au glucose administré par voie intra-veineuse ;

2) une courbe de glycémie de type diabétique à l'épreuve d'EXTON-ROSE (doses successives de glucose) ;

3° une résistance à l'hypoglycémie à l'épreuve de l'insuline intraveineuse ;

4) une augmentation du facteur anti-insulinique dans le sang et l'urine.

Tous ces troubles biochimiques se présentent parallèlement au syndrome mental et disparaissent avec lui. Le syndrome oniroïde est ainsi caractérisé par l'impossibilité de compenser une augmentation subite de la glycémie, et par la résistance à l'insuline intraveineuse.

Le syndrome oniroïde ferait son apparition chaque fois que le métabolisme hydrocarboné est altéré, soit parce que les enzymes sont inhibés (intoxications par les barbituriques, sulfamides, ou délires alcooliques), soit parce que le glucose ou l'oxygénation font défaut (hypoglycémie, vol à haute altitude, troubles de l'hémoglobine).

L'action de la convulsivothérapie sur le syndrome oniroïde consisterait en une diminution de la sécrétion hypophysaire secondaire à une augmentation de la sécrétion surrénale.

L'auteur tente une explication des psychonévroses en se basant sur l'action de différents produits pharmacologiques (barbituriques, protoxyde d'azote, éther, anhydride carbonique). Avec certains d'entre eux, la guérison peut se réaliser par un mécanisme psychologique de catharsis, quoiqu'il soit permis de penser que la drogue utilisée peut y contribuer biochimiquement d'une manière encore mal connue. Avec l'anhydride carbonique, l'action principale est celle du gaz sur le cerveau.

L'auteur décrit en détail la technique de l'administration de l'anhydride carbonique et les réactions du malade qui s'y trouve soumis. Le traitement est sans danger. Il consiste à donner par voie respiratoire un mélange de 30 % d'anhydride carbonique et de 70 % d'oxygène pendant 30 à 120 secondes, 3 fois par semaine jusqu'à un total de 20 à 150 séances. Cette thérapie est indiquée chez les malades avec symptômes de « conversion », dans la névrose d'angoisse avec sentiment de culpabilité ou

inadaptation et irritabilité, et chez les mésadaptés avec instabilité émotive. Les effets de l'éther sont analogues dans ces cas.

L'effet de tous ces médicaments est le même et identique, seul le mécanisme d'action chimique diffère.

L'auteur décrit enfin les effets physiologiques observés dans la thérapie par l'anhydride, et reproduisibles par l'éther. Par une action sur le neurone, augmentant son seuil de stimulation et diminuant la fatigabilité nerveuse, cette thérapie illustrerait l'hypothèse de la fonction homéostatique du cerveau, cette fonction étant perturbée dans les psychonévroses et permettant l'envahissement progressif des aires cérébrales inhibées par le processus pathologique.