Violent Behavior, Brain Dysrhythmia, and Glucose Dysfunction A New Syndrome

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The aim of this study was to test experimentally the empirical existence of the following syndrome: aggressive behavior, brain dysrhythmia, and glucose imbalance. Only patients exhibiting the above participated in this study. Subjects were divided into four groups: the Experimental Croup consisting of treatment for the dysrhythmia and hypoglycemia, and the Hypoglycemia, the Brain Dysrhythmia, and Other Medication Control Croups treated for the hypoglycemia, the brain dysrhythmia, and for neither respectively. Diphenylhydantoin and/or Pyridoxine was administered in cases of dysrhythmia, and a low-carbohydrate, high-protein, high-fat diet was given for hypoglycemia. Reduction in aggression as measured by a scale designed by the' Es *was used as the dependent variable. Amount of aggression was measured before and after treatment which lasted from one to four months. It was hypothesized that aggressive behavior, dysrhythmia, and glucose imbalance were related and that the treatment of the last two factors would cause the most amount of reduction in aggression. The predicted effect and the existence of a correlation between the three factors was found. All F values were significant at the .01 level.*

A theoretical assumption regarding a disturbance in tryptophan metabolism caused by an increase of insulin output was proposed. Further research is being carried on.

Human aggression as such is the most challenging problem that individuals and society must encounter today. Aggression as a mechanism of defense (as an instinctive reaction to an external aggressor) is accepted by social standards. However, if aggression is presented as an offensive force, then it is usually condemned by present moral rules. This form of aggression belongs in the areas of

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sociology, anthropology, or the ethics of human behavior.

Another type of aggression which is unanticipated and unprovoked has to do with medical pathology. Since it can also be precipitated by internal or external stimuli and show the same form of expression in many instances, it makes differentiation difficult. In order to speak of aggression from either a psychological or sociological perspective, it is important first to rule out a dysfunction of the brain, the basic organ of behavior. This paper will deal with aggression as a medical entity.

The use of neuroleptic medication has brought a better way of controlling aggressive behavior without the need of mechanical restraint. Yet, in many instances, major tranquilizers are not enough to suppress symptoms of aggression, thus suggesting that other mechanisms refractory to the action of tranquilizers are involved.

Many years ago, it was reported that diphenylhydantoin (D.P.H.) usually employed as an anticonvulsant was very effective in controlling psychotic patients with prominent symptoms of excitability, irritability, and aggressiveness (Kalinowsky and Putnam, 1943; Freyhand, 1945; Kubanek and Rowell, 1946; Turner, 1969). One study was negative after treating patients with character disorders (Klein and Greenberg, 1967). Our experiences have shown positive results with D.P.H. in non-epileptic psychotic patients with or without brain dysrhythmia (Diamond and Yaryura-Tobias, 1971), and also in a delinquent population with psychosis, neurosis, or sociopathic behavior with outstanding aggressive symptoms (Mallea et al., 1972). However, it was noticed that D.P.H. was ineffective in cases of aggressive behavior with a low glucose-tolerance curve and brain dysrhythmia. These patients presented the following triad: brain dysrhythmia, violent behavior, and functional hypoglycemia. Apparently the triad was not mentioned in the medical literature. Therefore, it was called the behavioral-gluco-dysrhythmic triad (Yaryura-Tobias, 1973). The aim of this study is to determine the clinical existence of the behavioral-gluco-dysrhythmic triad.

METHODOLOGY

Subjects

Forty-five patients (N = 45) seen on an outpatient basis at the North Nassau Mental Health Center in Manhasset, N.Y., and at Laboratorio de Psiquiatria y Psicofarmacologia Experimental in Buenos Aires, were used in the study. There were 19 females and 26 males ranging between the ages of 5 to 43 (x = 20.37). All **Ss** were diagnosed aggressive behavior with functional hypoglycemia and cerebral dysrhythmia. In addition, some received the following psychiatric diagnoses according to the manual of the APA: schizophrenia (23); personality disorder and certain other non-psychotic mental disorders (4); non-psychotic organic brain syndrome (7); neuroses (4); transient situational disturbances (2); and mental retardation (2).

Patients were not restricted to the two geographical areas where treatment was administered. They were residents of other states and places, indicating the diversity of the sample.

Materials and Apparatus

All subjects were fasted for 10 to 12 hours and then given a six-hour glucose-tolerance test (6HCTT) in which, after a fasting specimen was taken, 100g of glucose in a water solution was orally administered. Glucose level measurements were taken for two consecutive half-hours and then every hour. The Ortho-toluidine method was used predominantly and in a few cases the Folin-Wu and Somogyi method. The normal ranges were 60-100 mg, 80-120 mg, and 65-110 mg of glucose per 100 ml of serum, respectively. The 6HGTT response criterion was interpreted as positive for functional hypoglycemia if, (a) there was a blood sugar drop of 20 mg percent or more below the fasting blood

sugar level, (b) a drop below the low range reading of the method employed, and (c) an elevation of 20 mg percent or less, followed by a decrease of 20 mg percent or more below the fasting level (flat curve, Salzer, 1966; Beebe and Wendel, 1973; Sussman et al., 1966).

Electroencephalogram (EEC) recordings were asked of patients, and only those exhibiting an abnormal reading were included in the study. With those cases who had received other forms of therapy, the EEGs were matched with the time of their previous treatment, and an indication of their aggression was obtained from other doctors. Aggression was quantified by the two Es, and each S was judged according to the scale E designed. The scale is presented on Table 1.

Procedure

According to the scale presented Ss were considered aggressive if they were assaultive, had outbursts of rage, broke objects, were extremely impulsive, or had uncontrollable tempers. These were judged on the basis of Ss' and families' report and psychiatric and psychological evaluations. If these criteria were not outwardly manifested, but Ss reported thoughts of these actions, they were still considered aggressive.

An aggression score was recorded for the S at the time first seen by the E. Within one to four months an evaluation of the treatment was made and a second score was given. The difference between the two scores and the reduction in aggression was the dependent variable. In order to test the existence of the triad, it was necessary to determine whether the treatment of the brain dysrhythmia

TABLE 1 Aggression Scale

0 No aggressive behavior or thought.
1 Mild, 1 rage or thought per month.
2 Slightly moderate 2 or 3 thoughts or aggressive action per month.
3 Moderate, 1 thought or action per week approximately.
4 More than 1 aggressive thought or behavior per week.

and the hypoglycemia would result in a reduction of aggression. Also, it was necessary to test the effect of just treating one of the factors, the brain dysrhythmia or the hypoglycemia, or treating neither but just administering tranquilizers.

Subjects were assigned to either of four groups:

1. Experimental (20 Ss) where Ss were given a diet in addition to D.P.H. or pyridoxine (Py).
2. Diet alone (7 Ss).
3. D.P.H. or Py alone (11 Ss). D.P.H. orally 90-300 mg three times daily -Py (200-1000 mg) three times daily.
4. Tranquilizers (7 Ss).

Thus, there were three control groups other than the experimental group. Diet when given was low carbohydrate, high protein, high fat.

RESULTS

To verify the empirical existence of the behavioral-gluco-dysrhythmic triad an experimental procedure using four groups was set up. The mean reduction in aggression for each group was computed.

'As seen in Table 2, the Experimental Group resulted in the most amount of reduction.

To test whether there was a reliability between the means, a least squares analysis of variance was done on a multiple regression program. A simple, two-way analysis of variance could not be used due to the unequal number of Ss in each group. An analysis of variance summary table deduced from the regression program is presentedin Table 3. 184

TABLE 2

Mean Reduction in Aggression for the Four Groups

		DRUG given	DRUG not given
DIET	given	2.6	.29
	not given	.73	.58

TABLE 3

ANALYSIS OF VARIANCE
COMPARING THE GROUPS

Source	Sum of Squares	Degrees of Freedom	Mean Squares	F Value
Drug	21.9	1	21.9	27.95*
Diet	14.255	1	14.255	18.19*
Drug x Diet	10.92	1	10.92	13.94*
Error	32.125	41	.7835	

Note: *p < .01

TABLE 4

MULTIPLE REGRESSION SUMMARY TABLE
TESTING THE EFFECT OF DRUG AND DIET

Variables	Multiple R (Correlation)	Proportion of Variance $(R)^2$	Increase in R^2	F Value
Drug	.5259	.2765	.2765	16.4351*
Diet	.6756	.4565	.1800	13.9085*
Drug x Diet	.7710	.5944	.1379	13.9374*

Note: *p < .01 All increases were significant in an additive manner.

Since the statistical analysis was done on a multiple regression program the F values are to be interpreted as such; the drug's main effect and the diet's main effect were found to be significant. Also, an interaction effect was found between the two. To determine which specific group resulted in the most reduction of aggression, Tables 2 and 4 should be examined. The interaction implies that significantly greater improvement will be found when administering drugs to patients on a diet (2.6 - .29 = 2.31) than when the drug is administered to patients who are not on the diet (.73 - .58 = .15).

The Multiple Regression Summary Analysis on Table 4 shows that the combination of the diet and drug explains 60 percent of the variance. All the data confirm the existence of the behavioral-gluco-dysrhythmic triad.

In examining the cases, it was noted that 39 percent of the patients' blood sugar drop was below the normal range of the method employed. Approximately 39 percent had flat curves and 22 percent had a 20 percent drop from the fasting hour. EEG findings were represented by different pathological tracings without specificity, where one or more signs were present. Among them, small spikes, slow waves, and paroxysmal discharges were recorded. The main location was bilateral and temporal. Hyperventilation had at times activated the pathology.

DISCUSSION

The etiology of aggression is partially known from the medical viewpoint. Leaving aside the psychological aspects of aggression, we may begin to think in terms of variables related to the neuro-physiological mechanisms of the brain that will comprise histological, chemical, and/or electrical modifications. Those changes can be a direct expression of an illness dwelling within the cerebral structure or may be of an illness located, outside the brain.

The anatomical structures usually involved with aggressive behavior are those grouped under the limbic system -temporal lobe, amygdala, hippocampus, pyriform cortex, and hippocampal gyrus. Through hypothalamic pituitary connections, it links with automatic inborn responses, mediated by the autonomous nervous system and endocrines. That area might not suffer from tissue lesions, yet its chemistry might be impaired. For instance, glucose metabolism, calcium disturbances, endocrine factors, faulty nutrition, chronic use of brain intoxicants, such as alcohol, associated with vitamin deficiencies can produce altered behavioral states, at times accompanied by brain degeneration.

An interesting study cited that the brain, like the periphery, may have a glucose threshold which is also sensitive to insulin. Therefore, after an injection of insulin, glucose penetrated the brain at much lower levels than before (Butterfield et al., 1966). Also in that study done with volunteers, hypoglycemic symptoms - sweating, blurred vision, hallucin-

ations, and feelings of unreality - were observed in association not only with a low blood sugar level, but also with a low brain glucose-uptake. This would show the minor importance of blood sugar levels in the periphery which might not reflect the state of glucose in the Central Nervous System.

Also, it is a very well-known fact that severe hypoglycemia may cause convulsions with definite alterations in the electroencephalographic pattern. Yet, repetitive hypoglycemic reactions without convulsions may also alter the EEC pattern, and in children severe hypoglycemia, due to organic hyperinsulinism, will cause irreparable damage to the brain (Bell et al., 1970). Increased neuronal sensitivity caused by anoxia due to low blood sugar and also the same mechanism could bring episodes of hyperventilation which eventually would modify the EEC pattern already altered (Buckley and Cellhorn, 1969). In previous studies, a relationship between diabetogenic hyperinsulinism and brain dysrhythmia (Roberts, 1964b) as well as pseudohypoglycemia and abnormal electroactivity of the brain (Fabrikant, 1964) were described.

At this point, it should be discussed if the levels of glucose in the plasma are sufficiently low to produce brain dysrhythmia or whether the two, brain dysrhythmia and hypoglycemia, can coexist without modifying the other's physiology. Either way, these two factors are capable of causing or precipitating an outburst of aggressive behavior. From previous studies, it has been determined that aggressive behavior may also be a symptom of hypoglycemia (Yaryura-Tobias and Neziroglu, 1974). In those cases the degree of aggression varied, and in the casuistic bibliography even a case of homicide has been mentioned (Fricke, 1970). In all the cases reviewed, including our own samples, no correlation between glucose levels and intensity of aggression was found. However, the frequency of the attacks might be subjugated to the severity of the hypoglycemia.

The simultaneous presence of EEC abnormalities and functional hypoglycemia without clinical correlation could also be entertained, admitting that both factors could modify the patient's behavior concomitantly but without interdependency. Our results have shown that there is an interaction between D.P.H. and the hypoglycemic diet, though this does not imply that there is necessarily an interaction between brain dysrhythmia and hypoglycemia. It merely indicates an interaction between the two treatment forms, thus requiring both an anticonvulsive medication and a hypoglycemic diet. The addition of Py into the treatment of some patients seemed to be beneficial, probably explained by its anticonvulsant properties and close association with the functioning of the brain (Raine, 1969; French, 1969).

It would be of interest to know the mechanism of action between the EEG changes and glucose levels in the brain. In the rat, the injection of insulin or the consumption of carbohydrate causes sequential increases in the concentration of tryptophan in the plasma and of serotonin in the brain (Fernstrom and Wurtman, 1971). In massive myoclonic epilepsy it was found that the administration of tryptophan increased the excretion of xanthurenic acid. This finding was in accord with a deficiency of Py, and on the administration of this vitamin to the patient a definite decrease of convulsions and improvement in mental status was observed (Cochrane, 1959; Bower, 1961; Hughes et al., 1967). Such an increase of tryptophan could cause a decrease of Py, which is utilized in the Py-dependent steps in the metabolism of tryptophan such as anthranilic acid and 5-OH tryptamine. The increased consumption of Py, if severe, may produce convulsions. This would indicate the need to supplement our patients with massive doses of Py. Let us not forget that tryptophan, serotonin, and, in general, indolamines are usually related to behavioral changes.

According to the results already

described, it seems that the presence of aggressive behavior, hypoglycemia, and brain dysrhythmia constitutes a triad where the last two factors interact and seem to cause aggressive behavior. An integral treatment of D. P.H., Py, and hypoglycemic diet must be given in order to obtain a satisfactory remission of the symptoms.

We would like to advance a hypothesis of work, suggesting that the triad is originated in a disturbance of the tryptophan metabolism subsequent to a glucose imbalance perhaps related to the insulin output. As a consequence, Py depletion and also cerebral hypoxia causing hyperpnea would alter the electrical activity of the brain resulting in aggressive behavior, thereby altering the adrenalin output seen in stress.

We are aware that further studies are needed. For instance, we have examined several cases with all the clinical symptoms of the triad, yet we failed to register EEG abnormalities or hypoglycemic curves. It seems that in riots and urban violence, brain dysfunction is rather a common finding (Mark et al., 1967), though many people with brain dysfunction do not always exhibit violent or aggressive behavior (Pollack, 1967). It could be suggested that many cases with clinical symptoms of brain dysrhythmia have negative electroencephalographic recordings probably due to lesions in deeper regions of the brain not detectable by standard techniques. The same could be said of hypoglycemic states only demonstrated with the afternoon glucose-tolerance tests (Roberts, 1964a).

Whether this triad constitutes a new syndrome or not might not be as important as the consideration given to it for the proper diagnosis and treatment of aggressive behavior where other forms of therapy have failed. In this manner, the risk of performing unnecessary psychosurgery for uncontrollable aggressive behavior could be minimized.

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