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Some of the metabolic aspects of idiopathic epilepsy

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SOME OF THE METABOLIC ASPECTS OF IDIOPATHIC EPILEPSY

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Of all the major disorders which add to the list of human afflictions, epilepsy probably stands at the head of other disorders in social and economic significance. In a medically enlightened age we can say little more than Celsus, who when he saw epileptics drinking blood from the wounds of dying gladiators, exclaimed in effect, "What a miserable disease that makes such a miserable remedy." Hippocrates said of epilepsy, "Whosoever is acquainted with such a change in men and can render a man humid or dry, hot or cold, by regime could also cure this disease."

Lennox (63), who has devoted more time and study than any American worker in this work, has attempted to stress the subject to the lay and medical public. In his lay book, "Science and Seizures" he pointed out that statistics of the 1917 World War draft revealed that one in two-hundred had a history of seizures. He further estimated that 500,000 persons in this country are subject to seizures. This compares closely with the number of active tuberculosis and diabetic cases. Further, he states that for every one having a seizure, 20 have a predisposition to seizures as determined by the use of the electro-encephalograph. Approximately 50,000 epileptics are hospitalized at an estimated cost of $20,000,000 a year. The direct cost in 1939 was $100,000,000. If the economic aspects of epilepsy are surprising, the amount of public interest and the amount of active research conducted are even less hopeful. Since the year 1561 Lennox states that only 50 books have been written about epilepsy. In 1939 only 244

articles appeared in the literature and these comprised in the main the unusual or perplexing single cases. This figure compares favorably with literature reviewed since 1939. In contrast to the cost, only $25,000 to $30,000 a year is spent in research on this problem. The social and economic losses to the epileptic cannot be numbered.

However, research is not hampered alone by insufficient funds or lack of interest. Idiopathic epilepsy quite naturally falls under the specialization of neurology, but from the etiological standpoint of disordered metabolism the study is one for the biochemist. Consequently, the researcher in this study must be a competent neurologist and a biochemist as well as a good physiologist. Another difficult factor to overcome is lack of available material. Since epileptics are well people, except for their paroxysms, long time confinement for study is a difficult matter to overcome. This is most evident when we see in the literature numerous theories and conclusions drawn from studies of single or very few cases at the most. For this reason the main stress always will be given to the largest series of cases in this review.

It is the purpose of this thesis to review the literature on research which has consisted of the study of blood chemistry changes which are peculiar to the epileptic and which will influence frequency of seizures in a susceptible individual. This is an attempt to review the gross tissue fluid changes with the

thought in mind that these changes reflect only a very incomplete picture as regards cell metabolism.

Only indirect information can be gained from an analysis of the body fluids, the value of the observations being in inverse proportion to the distance of the fluids from the brain. An analysis of the blood entering and leaving the brain at the same time that the functional electrical activity is being recorded is the most direct information yet available about the metabolism of the brain cells which are discharging abnormally.

Some of the concepts toward which these studies are directed may be discussed here. Lennox, Gibbs and Cobb (55) state the problem in these terms: "Some disturbance of the brain exists in all cases in which seizures occur. The underlying phenomenon of essential epilepsy is a dysrhythmia which is the resultant of chemico-physical peculiarities of the discharging cells of the brain. Structural abnormalities of the brain, either genetic or acquired seem to be only contributory. Seizure discharges arise from live functioning neurones, and not from dead neurones. Peculiar to its origin, the peculiar chemistry of epilepsy is the chemical structure of the gene, which comes to be expressed in the chemical structure or the chemical reaction of the neuronal cells of the brain. Because no definite pattern of seizures can be elicited in any two patients it seems better to look upon each disorder as explosive in character, which is a general sudden widespread change such as may occur in a chemical

reaction and characterized by a simultaneous change involving all cells at once." By this latter statement it seems important to know the chemical blood status, since this should be the most constant factor influencing internal cell metabolism, and subsequent massive irritation of neurones due to this change. However, this is assuming that the seizure is due to irritation.

We realize and stress here that even though subsequent evidence will be presented to point out the same physiological abnormalities, there must be a tendency or susceptibility toward convulsions. Likewise, susceptibility is proved by observance of like changes in the patient and in the normal.

Many factors are known to influence seizures. These are anoxia, alkalosis, hypoglycemia, and hydration of the blood. It is then better to see what processes affecting the brain as a unit organ of more or less homogenous cytology might be responsible for convulsive phenomenon. Obviously the nervous system has certain properties common to all its different parts such as temperature, pressure, concentration, electrical potential, and pH. It has further been suggested by Lennox and Cobb (55) that perhaps it is not an irritation but rather a temporary functional destruction of motor cells. The labile nature of nervous tissue metabolism will be stressed later in this connection.

The study must be limited. It seems well to limit the scope of this paper to the metabolic changes coincident with the frequency of seizures. An attempt will be made to clarify the

concepts of carbohydrate, protein, and fat metabolism in the epileptic as compared with that of the standard normal. Where possible, interval blood findings, chemical variations, during or immediately preceding the seizure, and variations following the seizure will be given. In addition, the effect of induced changes in the blood constituents will be given. A special section to the ketogenic diet will be included following the starvation treatment. With the introduction of the electro-encephalograph a new era of investigative methods has been opened, since 1929 when Hans Berger (5) introduced this device. Since 90 per cent of the epileptic patients display disturbance of the brain waves, which may be known as asymptomatic dysrhythmia in the interparoxysmal period, it would be very helpful if all of the work done before 1929 had been accompanied by the use of the electro-encephalograph. Blood chemistry before 1920 was erratic, but with the use of colorimetric determination by the method of Folin and Wu, a consistency of results may be expected following a period of unfounded speculations and wishful thinking. Therefore, work before this time will be given only for its historical value. With these limitations in mind we shall begin.

Since the definition of epilepsy is in as much confusion as the essential nature of the disease, it will be well to clarify the use of the term in this paper. Wechsler (102) states that epilepsy should be considered a symptom complex and not a disease entity. Probably the "convulsive state" is a better term and is

meant when using the word "epilepsy" or "seizure" in this thesis. This includes the entities grand mal and petit mal.

CARBOHYDRATE METABOLISM

Since the introduction of insulin in the control of diabetes mellitus and the subsequent experimental production of hypoglycemic shock with this hormone, considerable attempt has been made to show the relationship between hypoglycemic shock and epileptic seizures.

Hypoglycemia has long been known to cause convulsions. MacLeod (69), discussing explanations which have been given for this phenomenon, believes himself that the convulsion in hyperinsulinism is due to rapid changes in tension of glucose in the nerve cell. He points out that symptoms of hypoglycemia are much like those of anoxia and that convulsions may be caused by a locking of oxygen within the tissues with consequent deficient oxygen of the blood entering the brain. In 1925, Forshay (26) confirmed this in showing that the symptoms of the reaction from insulin accompany a fall in the sugar content of the cell rather than the plasma. If this is true, the blood content of sugar reflects the true state of affairs only partially.

Asher and Takakoshi (4) in 1925 showed that methods which reduce glycogen of the liver and muscle by 90 per cent, reduce glycogen of the brain by only 20 per cent. They found that convulsions produced by insulin injection could be produced only by

lowering the glycogen content of the brain 80 per cent. They concluded that storage of carbohydrate in the brain is peculiarly stable and that it is drawn on by conditions that favor a state of exaggerated excitability of the central nervous system. Therefore, the state of hypoglycemia as far as the brain cell is concerned, which is probably most important, is an effect rather than a cause of the convulsive state.

Lennox (59) in 1927 stated that an abnormality in sugar metabolism is suggested by the fact that convulsions and increased irritability of nerves accompany low blood sugar while diminution in glycogen content of the brain accompanies convulsions. Furthermore, he stated that there was clinical improvement in variation in blood sugar levels.

Greisheimer (36) in 1925 observed that frog nerve preparations lost their irritability and conductivity when immersed in cane sugar solutions. This fact has been confirmed many times and is used in simple laboratory studies in physiology in study of nerve irritability. Greisheimer also used decerebrate dogs. The irritability of nerves was tested by using the weakest break shock necessary to give a response in the femoral and radial nerves. Irritability consistently increased as the blood sugar fell. This occurred in peripheral nerves and in the reflex arc.

Many years before brain metabolism was studied, many attempts were made to show that the epileptic was influenced by increased irritability of the central nervous system caused

by low sugar levels of tissue fluids. The fasting blood sugar, the glucose tolerance, and high carbohydrate feeding were the early laboratory attempts made toward the answer to this problem. With more moderate conceptions of brain metabolism and with the additional aid of the electro-encephalogram more recent findings are more important.

Before reviewing the work on the fasting blood sugar and sugar tolerance curve it must be stated that most of this work was done without discrimination between arterial and venous blood. Few investigators stated from what part of the circulation the blood came, although in almost all cases the method of determination was given. It seems very discouraging to know that it was 1927 before Myserson (76) pointed out the fallacy of former measurements. He logically assumed that it seemed theoretically correct that brain metabolism could be better studied if one could study the blood directly before it reached the brain and then could study it directly as it came from the brain, without the admixture of blood coming from other parts of the body. He outlined a simple method for tapping the carotid and jugular veins for this purpose. His method was followed by further studies into the respiratory quotient of brain tissue.

Fasting blood sugar:

A considerable number of investigators have attempted to prove that seizures are associated with low blood sugar levels.

Kooy (53) in 1919 studied the fasting blood sugar in eight patients with epilepsy. He used no control cases. Although he found variation in blood sugar he attributed this to emotional influences and, therefore, considered his results of no consequence.

Frisch and Fried (27) studied three cases, making 39 measurements. They found blood sugar levels varied with individual patients during the critical period.

Burgh (9) and co-workers in 1924, studied four cases which are to be mentioned because of the very careful method of investigation he used. Using the colorimetric test of Folin and Wu with venous blood, they found quite consistently low blood sugar values, considering fasting levels below 80 mg.% as significant. They concluded from this study that hypoglycemia may be correlated with epilepsy.

Holmes and Holmes (45) in 1925 studied blood sugar more directly by using arterial blood directly from the brain. They found that inducing hypoglycemia caused no marked change in the amount of reducing substance in the brain tissue. The reducing substance was not capable of forming lactic acid, however, and therefore, probably was not glucose. This finding was confirmed by Cori and Cori (14). These studies seem to indicate that even though a tendency toward hypoglycemia might exist in epileptics, it had little real significance in reflecting brain tissue metabolism.

In 1926, Tychowski and Crowell (99) approached the problem

in a different manner. Since hydration of the brain cells is known to induce seizures, the influence of induced seizures by hydration was studied. They found that hyperglycemia accompanied an increase in intracranial pressure, so that theoretically a condition of hypoglycemia seems to have little significance when considered in this way.

Among other metabolic studies in epilepsy, Wuth (107), in 1926, studied the blood fasting levels in ten epileptics. He found all within normal limits. In a further study of forty cases using ten controls he found normal values again.

It might be mentioned here that the limits of normal varied with each investigator and that in addition to different methods of finding blood sugar levels, different constants of normals were used. The general range, however, was within the level of 80 mg.% to 120 mg.%. Realizing the discrepancy of results, most investigators were liberal in their variations and attempted to standardize their results with their own normals.

In 1927, Lennox (62) made the largest study yet on the fasting blood sugar levels in epileptics. Reviewing the knowledge up to this time he pointed out that the symptoms of hypoglycemic shock are usually manifest in normals when sufficient insulin is given to lower the blood sugar to 45 - 50 mg.%. He then stated that his problem was to determine if persons, subject to recurrent convulsions, have abnormal concentrations of blood sugar. He studied 267 patients, all with idiopathic epilepsy, and spread

throughout a satisfactory age and sex ratio. Since barbiturates diminished the frequency of convulsions he attempted to find the influence of this drug on blood sugar. He found no effect. Lennox made 2,000 measurements on his group. He hemolyzed the blood immediately and used a low oxalate content to prevent distortion of his findings. He made determinations before breakfast in 66 of his group, and 24 hours after taking food in 201. He found the greatest frequency of blood sugar concentrations to be around 90 mg.% as compared with 100 mg.% in an equal number of normals. His epileptic group showed fewer lower values than his controls. He concluded that the fasting blood of persons subject to convulsions does not show abnormal concentrations of sugar. Quoting Kersten (5), Lennox found that he was of the opinion that the time relationship of blood sugar to convulsions may be of some importance. Kersten in 1921 found low blood sugar values in the group one half, or one hour preceding seizures, and higher values during the several hours following seizures. This was not a constant relationship, however. Lennox suggested that the rise following the seizure was due to the mobilization of glucose from the liver by the adrenalin liberated during motor activity.

Lennox thought that one should expect low sugar levels in the blood to be accompanied by increased frequency of seizures, since there is a relationship of hypoglycemia to convulsions, since there is increased irritability of nerves with low sugar values, and since diabetes and epilepsy combined in one patient

is a rare finding. He found the reverse to be the case because in his series induced low blood sugar levels seemed to reduce the frequency of seizures. In one patient Lennox found that giving enough insulin to cause a drop in blood sugar of 72 mg.% decreased the number of seizures, while giving enough sugar to raise the blood sugar to 160 mg.% caused no increase in the frequency of seizures.

The blood sugar level during the seizure, Lennox pointed out, according to previous literature was conflicting and fragmentary. Believing that this was possibly due to the factor of muscular exertion he did a very interesting experiment. Knowing that muscular exertion will in itself cause hypoglycemia, and that axphyxia will also cause an increase in blood sugar, he used a healthy subject to simulate the convulsive attack of the epileptic. Withdrawal of blood in different phases of convulsions revealed that in the epileptic patient the blood sugar did not vary over 3 mg.% from 80 mg.% during the seizure. In the healthy sugject a rise in blood sugar occurred during the clonic phase and continued 5 to 30 minutes afterwards. This suggested that the epileptic was unable to mobilize sugar at a time when needed and indicated the therapeutic value of giving glucose to the status epilepticus. He concluded that a study of 267 epileptics failed to show abnormality in the concentration of sugar in the blood or any direct relation between the blood sugar level and seizures. In addition, he concluded that the blood sugar level

was secondary to changes in blood alkalinity and that the latter was of more importance in the concept of etiological importance. His final conclusion was that possibly epileptics show a tendency toward low fasting blood sugars since few high values were found.

In 1928, Lennox and Cobb (55) reviewed the literature up to that date. They found that the majority of opinion was that the blood fasting sugar level was of no significance as far as the association of low values in epileptics was concerned. They stated that apparently a minority of patients responded to the administration of glucose for which the explanation is obscure.

Munch-Peterson and Schou (74) studied 166 patients in 1931. They found 5 per cent of their group had fasting blood sugar levels of 60-69 per cent of glucose; 26 per cent had 70-79 mg.% glucose; 45 per cent had 80-89 mg.% glucose; 22 per cent had 90-99 mg.% glucose, and one per cent had 100 mg.% glucose. In spite of these rather low values they attached little real meaning to their findings.

In 1934, Nielsen (77) studied 58 mixed cases of essential epilepsy. He believed his patients had a periodic, and in some cases, a constant tendency to show a low sugar content.

Huury and Hirschfelds (38) in 1935 made three determinations each on 25 mixed cases. Their study is notable because they made determinations before, during and after convulsions. Each case they found within normal limits. They found the rise in blood sugar during the seizure to be proportional to the severity

of the seizure, and after termination of the convulsion, the blood sugar returned to normal in 2 - 4 hours. Hypoglycemia was not found in any case.

Pollack and Bosher (85), in an extensive review of this subject in 1937, stated that their criticism of the literature was that there were an insufficient number of controls used in conjunction with studies on epileptic patients. Because of the variability in methods of blood determination and institutional conditions, the use of controls seemed a necessity to them. They stated further that a larger series of individual conditions must be studied so that when values are found that are higher than those for a large series of normal subjects, the significance may be determined.

Goldstein and McFarland (34) have made a complete review of the biochemistry of epilepsy. The reader is referred to this work for a more complete and detailed analysis of all the biochemical aspects of this problem. They quoted 36 investigators with a grand total of 824 cases. Twenty-nine investigators, including the largest series by Lennox, showed normal blood fasting sugar values. Two stated emotional influences predominated. Two stated that hyperglycemia existed. Three stated that hypoglycemia was present, and three other investigators were undecided.

The glucose tolerance curve:

The investigators prompting this study were engendered by the same reasons as for the study of the blood sugar fasting level. Investigators in many cases studied the tolerance curve in conjunction with the blood fasting level. The same difficulties and criticisms have been directed toward this phase of the problem.

Kooy (53) in 1919 found in eight patients studied that there were normal sugar curves following the ingestion of a breakfast consisting of bread, butter and milk. In a further study of six patients, he stated that the immediate emotional status of the patient influenced results. He attached no significance to his study.

Schwab (93) in 1922 found normal curves in ten patients. The amount of glucose given is not available since the report was obtained from Lennox (55).

Holstrom (46) in 1924 took blood at intervals during the day from three patients given food every hour. He stated that seizures come at the low point in these curves. This investigator considers variation secondary to perturbations in the sympathetic nervous system.

Drury and Morn-Ridge (21) in 1925 studied fifteen cases and found normal blood sugar curves in all cases. They made their study giving a fixed amount of glucose by ingestion.

Lennox (59) made an extensive study of 140 patients with 400 curves, in 1927. He found that 37 per cent were higher

than normal at the peak of the curve. Fifteen per cent were lower than normal at the peak of the curve, and 48 per cent were normal levels at the peak of the curve. He stated that it was difficult to know whether or not abnormalities might possibly be due to individual differences in absorption and utilization of ingested carbohydrate. He noted that a review of the literature revealed that extirpation of the pituitary gland caused an elevation in the peak of the glucose tolerance curve in 27 out of 34 cases. In his series, frequently repeated curves gave an abnormal variation in sugar tolerance. He suggested that the coincident variability in function of the sympathetic system may cause consequent changes in blood flow or in activity of endocrine glands. His conclusions were that the data he collected, and all previous data, gave no evidence of abnormality of carbohydrate metabolism that might in itself cause seizures.

Munch-Peterson and Schou (74) in 1933 found a tendency toward flat curves in 25 patients studied. This is in direct contrast to the work done by Lennox, who found only 15 per cent of his patients having a low level at the peak of the curve.

In 1934, Nielson (77) studied 58 patients. Fifty of these failed to show a rise above 120 mg.%, and 15 failed to show a rise above 100 mg.% in the first half hour. Thirty-four failed to show a return to the fasting level at the third hour and in 11 the lowest point occurred in the fourth hour. In spite of these rather constant findings, he believed disturbed carbohydrate

metabolism was not a factor in the etiology of epilepsy. Nielson pointed out that his method of determination agreed with many other investigators using the same method.

Pollak and Bosher (85) in 1937 made studies of the glucose tolerance in 57 epileptics. They found 26 per cent had higher values at the peak than normal; 21 per cent were low, and 53 per cent were normal. The curves could in no case be related to the incidence of attacks or to the type of epilepsy. Both organic and idiopathic cases were studied.

Goldstein and McFarland reviewed the work of ten investigators. Four hundred and thirty-five patients were studied. Nine out of ten of these investigators found that sugar tolerance curves were entirely normal. One investigator found a tendency toward a flat curve.

The method of administration of the test meal was not uniform in most cases and, in view of this, the lack of adequate controls makes most of this study rather useless. As Lennox (59) stated, there is an individual variable of absorption and utilization in all people.

Schou (92) utilized this fact in his study of 100 cases of epilepsy. He stated that alimentary hypoglycemia can be demonstrated in 40 per cent of a non-selected group of patients, provided blood sugar levels are determined for four hours. This work was reported in 1937. Thirty per cent of his group showed a fasting level of 60 mg.%; 34 per cent, a maximum rise of less

than 120 mg.%; and 43 per cent, a level below 50 mg.% after four hours. He believes there is a fasting level below 60 mg.%, and a maximum rise to less than 120 mg.%, or a fall below 50 mg.% after four hours. He found that in those cases in which it did occur, this was a constant finding. Alimentary hypoglycemia occurred mainly in the younger patients with a relatively short duration of seizures. In 29 of the patients with low sugar surves, the average incidence of the seizures in 24 hours was calculated for 15 years and plotted on a curve in terms of number of seizures per hour. The curve showed two absolute peaks, one from 6 - 8 A.M., and one from 9 - 12 P.M. Two relative peaks were also plotted, one from 11 - 1 P.M. and one from 5 - 7 P.M. The 6 - 8 A.M. and the 11 - 1 P.M. periods seemed related to periods when hypoglycemia and seizures were coincident. The author considered this finding of such importance that he suggested extirpation of the pancreas or an exceedingly high carbohydrate diet to control seizures.

Wechlser (101) has said the latest word in this problem. He stresses that the hypoglycemic fit and the epileptic seizure differ in that in the latter the aura is present, convulsions are typical, there is complete loss of consciousness, termination is rapid and onset is immediate. In hypoglycemia, onset is slow, the convulsions are not typical, and unconsciousness is usually incomplete.

Brain metabolism:

The last ten years have seen tremendous strides in the understanding of nervous tissue metabolism. The newer work tends to discredit the gross biochemical changes manifest by the amount of metabolic constituents in the blood. It is not the purpose of this paper to develop the present concepts of brain metabolism, but it is the purpose to find the influence of nervous tissue metabolic changes in causation of idiopathic epilepsy. For this reason some understanding of the basic metabolism of the brain must be known.

Many workers are of the opinion that the single source of energy of brain tissue is glucose, since the amount of carbon dioxide produced is equal to the amount of oxygen consumed. In other words, the respiratory quotient is unity. Some of the first work in this study was done by Himwich and Nahus (42) in 1932. Many investigators confirmed this early work. In almost all instances the method of determination of blood gases was that of Van Slyke, using jugular and carotid blood. The oxygen and carbon dioxide tension has been determined in many animals in this manner. Handley, Seeney, and Scherman (39) believed that a fallacy lay in vivo experiments because of arterial anastomosis in the head and venous return flow from structures other than the brain. Consequently, they used a perfused dog's brdin from which other structures than the brain were isolated. They used the lung preparation of one dog to control and measure gaseous

exchange in the isolated brain section. They found the respiratory quotient to be 0.94.

In view of these facts, we may postulate that diminished oxygen or diminished glucose will inhibit the metabolism of brain tissue and in some way alter the electrical activity of the brain. Whether this change is due to altered permability of the cell membrane or due to changes in the tissue fluid media is important to know. We must also know how well the blood findings reflect the conditions present within the brain cell at a given time. Only by knowing this can we evaluate all past work done in blood chemistry studies, especially those directed at glucose metabolism.

Cori and Cori (14) in 1925 attempted to study this last problem following the observation that injection of glucose caused a corresponding rise in liver glucose. How did injection of glucose or insulin affect the glycogen and glucose content of brain tissue? They showed that insulin, sufficient to cause a hyperglycemia, did not lower the free brain sugar to an appreciable amount, although kidney and liver sugar were lowered. This suggests that it is improbable that hypoglycemic symptoms after an insulin injection are due to the lowering of glucose tension in the brain centers.

Best and Taylor (6) state the reverse: "Glucose is present in the brain tissue in about the same concentration as in the blood ..."

Dixon (20) in 1940 found that increase in glucose consumption caused increased nervous activity. They suggested that glucose depletion was a result of factors leading up to convulsions, such as anoxia and cyanide poisoning.

Gibbs and Lennox (31) in 1938, using the electro-encephalograph as the method of study, stated that the changes in blood oxygen and glucose did not cause significant alterations in the cerebral circulation. They placed more emphasis on the amount of blood entering the brain, which was influenced by the carbon dioxide content of the blood. The rate of metabolism is apparently proportional to the amount of blood. A gross hypoglycemia, however, caused a slowing of waves in the cortex.

Kerr (49) in 1937, approaching the problem in a different manner, induced convulsions and found no change in the carbohydrate fractions in the brain.

Lennox and Gibbs (56) in 1940 stated there was positive proof that a deviation from normal glucose metabolism of the brain occurs in patients with petit mal attacks. They said these patients tend to have a carbon dioxide production which is low in relation to oxygen consumption, or a lowered respiratory quotient. They maintained, however, that glucose alone was utilized and only explained their finding on the theory that perhaps glucose consumption is lowered in direct proportion to the amount of carbon dioxide produced, but could not determine what happened to the oxygen that was lost. This determination was made on gross

blood studies and the factor of cellular permeability must again be included in offering an explanation for this finding.

Along somewhat similar lines, Yakovlev's theory (108) of autonomic dissociation is interesting. He stated that there is a dissociation in rhythm and rate of energy metabolism within the internal medium. This dissociation in rate between the activity of the sympathetic and that of the parasympathetic divisions of the catabolic over the anabolic phase of energy metabolism in the nervous system. The catabolic release of energy is out of proportion to the restitution of energy in the nerve cells and this leads to a discharge of energy through inordinate activity of the effector organs of the cerebrospinal nervous system. In addition, the same dissociation in time and rate of the catabolic and anabolic phase of energy metabolism in nerve cells leads to the dissociation in time and rate of excitatory and inhibitory impulses at the synapes between nerve cells with a resulting prolonged refractory state of the cells. This theory seems to be pure speculation and there is no available proof for the statement.

The electro-encephalograph and carbohydrate metabolism:

Since the epileptic state is characterized by a constant pattern of brain wave potentials which exist without necessarily an associated seizure, the electro-encephalograph is an instrument which is very useful in determining immediately what effects small changes in the blood chemistry have on changing the pattern

of seizures.

Many recent investigators have shown that changes in blood glucose have an effect on the encephalogram of epileptics and normals. Hoaglund (43) and others have found lowering blood sugar by insulin resulted in lowering brain glucose with a consequent diminution of alpha frequencies. Injection of glucose caused the alpha frequencies to increase. Himwich (41) and others in 1939, confirmed the fact that diminished glucose caused a diminished frequency of the alpha rhythm which they interpreted as a slowing of brain metabolism.

Lennox and Gibbs (32) are of the opinion that the blood sugar level has more direct bearing on the petit mal cases, expecially in the younger age group. They used a mixed group of 34 patients with both grand mal and petit mal manifestations. They injected 60-100 units of insulin followed by dextrose and noted the intervening electro-encephalogram tracings. In no cases were seizures precipitated by hypoglycemia and they saw no increase in the grand mal type of activity. However, they saw a tremendous increase in the wave and spike activity of the petit mal patients when the blood sugar fell below 50 mg.%. In normal subjects they found that 50 mg.% glucose level is by no means low enough to precipitate this type of activity. Hypoglycemia then precipitates these waves only in those showing this type of epilepsy. They found a similar effect with hyperventilation, but similarly it did not occur in those patients who had either pure grand mal

manifestations or in those mixed cases of grand mal with petit mal where lowered blood glucose had precipitated the increased wave and spike activity.

Rubin and Turner (91) in 1942 reported that increases of blood sugar caused a slower frequency of slow waves and decreasing blood sugar caused faster waves to appear which they thought significant in the grand mal type of activity.

Davis (17) in 1943 induced hypoglycemia by insulin administration. He found a fall in blood sugar and hyperventilation accentuated the preexisting dysrhythmic tendencies. These two factors, he believed, had a synergistic action in producing slow waves. He found that high blood sugar and a low carbon dioxide level prevents this slowing. Lennox and Gibbs admitted the truth of this in their mixed cases, but not in their pure petit mal types, where a low carbon dioxide level alone would produce increased petit mal activity. Davis stated that hyperventilation and low blood sugar could reveal latent electro-encephalograph changes. In 43 observations, Davis (18) also found that slow swings of 2-5 per second in the frontal and precentral leads occurred. He stated that similar responces are found by stimulation of the vesticular mechanism and so related to changes in the skin and autonomic nervous system. Consequently, neither insulin nor hyperventilation induce dysrhythmia equally in all electro-encephalograms. As the blood sugar fell to 35-85 mg.% the normal alpha activity of the electro-encephalogram was increasingly replaced by slower waves, chiefly in the 6-8 cycle range.

Engle and others (24) in 1944 reported that the electro-encephalograph was important in "attempting to gain a threshold concept upon which diseases processes can be based." After intravenous infusion of dextrose they found a shift toward a faster frequency, and with falling levels of dextrose a shift toward slower frequencies. The inhalation of 100 per cent oxygen for five minutes or longer resulted in a shift toward faster frequencies. Apparently, he found induction of hyperventilation was not too significant in the influence of blood sugar changes.

Brain metabolism of glucose resembles in some respects that of other tissues in that lactic acid is produced in the absence of oxygen for resynthesis of glucose stores. However, the rise in lactic acid is very slow and when oxygen is admitted, the decrease is very slow. Gurdjean (37) found a definite slowing of waves corresponding with the rise in cerebral lactic acid. The electro-encephalogram showed increased amplitude and frequency with oxygen administration. He believed oxygen tension more important than carbon dioxide and glucose blood levels.

A considerable amount of work must be done before a conclusion can be reached on these studies. Indications are that study along these lines holds a great deal of promise.

PROTEIN METABOLISM

In this study it is difficult to summarize the findings of earlier investigators because of the variety of chemical methods used, some of which are now considered obslete, and because of discordant results obtained. The first studies into the metabolic aspects of essential epilepsy were those concerning protein. This was probably due in most part to the fact that the etiology of the convulsions of uremia was known first. The relationship of retention of non-protein nitrogen products to convulsions was known early. Naturally, the attempts to explain the convulsions of epilepsy were first aimed at disordered protein metabolism.

The first mention of protein influences was probably made by Gowers (35) in 1881, when he made mention without any basis for his statement, that a meat-free diet in many cases decreased the frequency of attacks.

Haig (38) in 1897 stated seizures were due to retention of uric acid in the blood. The fallacy of this proposition is seen in the recent studies in fasting in which there is an increase in the uric acid content in the blood, associated with a diminished frequency of seizures.

Lennox and Bellinger (55) in an exhaustive review of the subject, stated that information concerning incomplete or abnormal metabolism of protein substances can be gained only by careful measurements of the protein constituents in urine, feces, blood and expired air under controlled conditions of diet and activity.

Before the discovery of insulin and its use in the production of hypoglycemic convulsions there was widespread unanimity of opinion that persons with epilepsy had either a derangement of protein metabolism or a peculiar susceptibility to food.

Allers and Sacriston (3) in 1913 studied four patients in periods of 4 - 25 days each, recording urinary nitrogen, urea, uric acid, purine, and phosphates. There was noted a fluctuation in nitrogen excretion. In some instances an apparent negative nitrogen balance existed.

Pighini (84) in 1913 studied intensively the nitrogenous constituents of the urine and, in addition, the effect of injections of nucleic acid. His results were negative.

Rhode (88), Lennox (55), stated, in 1915, studied three patients with idiopathic epilepsy. One of these showed a positive nitrogen balance during two periods of study. He found that this single patient consumed 17 grams of nitrogen more than he excreted in a 40-day period. Half of this could not be accounted for by an increase in weight. Controlled studies are absent in this report.

Obrega and Urechia (78) in 1914 found increased blood urea before seizures with subsequent decrease after the seizure. Cuneo (16) in 1914 found a proteo-albumose in epileptics. He theorized that since glucose is necessary for synthesis of normal serum albumin, a lack in glucose causes production of albumose which produces convulsions. Albumose is an insulin-like substance.

This is an interesting theory and more remarkable that the study was made before the true nature of insulin was known.

Boultier (55) according to Lennox, in 1920 noted that there was a retention of nitrogen products in idiopathic epilepsy, but believed that this was an effect, rather than a cause, of seizures. Dufor (22) in 1920 noted in 15 out of 20 patients that the blood urea was about two times normal 12 hours before an epileptic seizure took place. The details of food intake along with time of seizures were not available in this report.

Weston (104) in 1920 made studies on ten demented epileptics under a constant hospital regime, so that there was little variability between individual patients. Weston measured the total blood nitrogen, the non-protein nitrogen, uric acid, urea nitrogen and creatinine. His results showed no abnormality in concentration of nitrogenous constituents in any period related to seizures.

Bisgaard and Norvig (7) made studies of the blood ammonia in 16 cases in 1921. They found blood ammonia levels ranging from .08 mg.% to .083 mg.%. They consistently noted a rising ammonia level beginning three hours before seizures, reaching a peak often three times the normal levels, just before the onset of the attack. They found the lowest values after seizures. Their beilef was that in essential epilepsy the neutralizing regulating factors are greatly altered. Felsen (25) criticized this last work believing the high ammonia values found by the above workers was due to the methods used.

Wuth (107) in 1922 studied in great detail 40 cases. He found a large number of abnormally high serum protein values as well as a great variability of this constituent in his patients. The serum albumin was consistently high, usually in the range of 8 - 8.5 gm.%. Wuth was probably the first to attribute the altered protein metabolism found by many before him to the increased muscular work and high blood pressure coincident with seizures.

Meyer and Bruhl (72) according to Goldstein, in 1922, studied 16 cases which gave evidence that the serum albumin shows great variations both in the seizure free period and in relation to attacks. They found, however, no relation between the kind of motor effects and the height of the serum albumin content. High serum albumin was found where no motor effects were seen. On the other hand, low albumin was associated with the increased motor effects.

Bruhl (8) working independently, reported in 1923 that he had confirmed this finding in 24 additional cases. He again related low serum albumin to high degree motor convulsions, but did not explain the causual relationship. In addition, five out of nine patients showed increased creatinine at the time of seizures. Inconstant increases of creatinine continued up to 2.16 mg.% after seizures. Bruhl attributed these findings to the convulsive mechanism and not to the nature of the attack.

Weeks and co-workers (103) in 1923, approached the problem of the effect of diet in the epileptic and, among other types of

diets, attempted to find the value of protein ingestion. To a group of six old age, institutionalized epileptics they fed a pure protein diet for 48 days. The number of convulsions before, during and after this regime were in the corresponding ratio of 100, 80 and 60. These investigators did not think that this was of much importance because of the general variability of their results. These workers experienced considerable difficulty in study on this group and suggested their experiments be repeated on a more hlpeful group of younger patients.

Lennox, O'Connor and Wright (61) in 1924 attacked the problem through the study of non-protein nitrogen variabilities. They reviewed the literature up to the time of their study and remarked that the only constancy in past work was the inconsistency of results. They pointed out that analysis of past work is difficult because of variation in results, and because of the variety of methods of determination used. Much of this past work had its basis of fact in the theories founded on the retention of non-protein nitrogenous products in toxic nephritis and eclampsia which is manifest in its more acute stages by convulsions. One hundred and twenty-nine patients were studied, average age being 42. Twenty-five controls were used. No organic diseased cases were admitted for study. These workers found normal non-protein nitrogen, normal urea nitrogen, and normal amino acid nitrogen in the blood. Since considerable emphasis had been placed on the fact that increase of uric acid accompanied the fasting state with

subsequent diminution of attacks, these workers believed that uric acid changes were entirely due to changes in diet. They found that high uric acid concentration up to 16 mg.% was not associated with an increase in the nujber of convulsions. No significant variation was found in average figures obtained from blood drawn within 24 hours before or after a convulsion.

Luck (34), according to Goldstein, in 1925 made a study of the ammonia in the blood of epileptics. He studied ten cases using fifteen controls. He found that the blood ammonia values in patients were about twice as high as controls. He concluded that this was not a cause of seizures, but failed to explain the significance of his finding.

Meyer (72) again in 1925 in a study of 15 cases found an increase in serum albumin as compared with serum globulin.

Wuth (107) in 1926 made another study of this problem. This time he came to the conclusion that blood creatinine, residual nitrogen, uric acid, average globulin-albumin ratio were within normal limits, but he still found great variability in serum protein.

Further confusion was caused by Frish and Fried (27) in 1926, who stated he found an increase in serum albumin before seizures and increased serum globulin after seizures. Lennox and Allen (61), in a study of 100 cases, found that 34 per cent of their cases had a fibrin content considerably above normal.

Felsen (25) studied 50 epileptic patients in 1930 and found

the blood taken immediately after the seizure showed no changes other than those which might reasonably be ascribed to physical exertion.

McKenzie and Chesney (67) in 1935 found decreased serum globulin and serum albumin after seizures in 29 cases of essential epilepsy. They found normal blood values for all other nitrogenous constituents.

Goldstein (34) reported that Peotrowski, studying 11 cases with seven controls, also found a higher total albumin level following seizures. Goldstein may be gainfully referred to for a complete statistical study of this problem. He has found throughout America and foreign literature that 18 investigators, studying 943 cases between them, came to the conclusion that there are no significant protein or nitrogenous changes in idiopathic epilepsy.

In the last five years some very interesting work has been accompanied with the study of protein-like substances in the blood, not directly related to metabolism, but nevertheless essential to normal physiology.

Kopeloff (52) has induced seizures by adding antigen to the cerebral surface of a previously sensitized animal. Luminal and dilantin reduced the frequency of attacks. Murray and Hoffman (75) in 1940 found that blood guanidine, an essential amino acid, was increased in every patient he studied. Sixty per cent had an increase during the aura, 100 per cent during the seizure, and about 10 per cent during the post-convulsion period. It is rather well

known that guanadine is a convulsive factor. These workers believe guanadine acts on the neuromuscular junction to cause a tetanic-like contraction. They believe, however, that guanadine is a result, rather than a cause, of the convulsion.

Cohen (12) and others in 1943, reported on their study of the convulsant effects of azosulfonamide, and noted a decreased carbon dioxide tension associated with the seizure, but thought that the carbon dioxide decrease had little direct effect because the administration of ammonium chloride did not acit as an anticonvulsant in these cases. They noted a decreased ammonia excretion during treatment associated with lowered blood carbon dioxide tension. With phenobarbital administration they found increased urine urates with diminished convulsions, and a lowered carbon dioxide tension. They believed the mechanism of action of azosulfonamide was due to its inhibiting action on carbonic anhydrase with consequent decrease in bicarbonate absorption at the renal tubule. Since Gibbs and others found that an increase in carbon dioxide tension prevents petit mal attacks, this drug has an anticonvulsant action in spite of the adverse carbon dioxide condition. It might suggest a high tissue carbon dioxide tension.

Waelsch and Price (100) Studied the biochemical aspects of glutamic acid therapy recently. With administration of this amino acid in 20 petit mal patients, they found decreased frequency and severity of attacks. This acid is synthesized by the body and transamination and rapid metabolic transformations of the acid

occur with ease. Glutamic acid is perhaps necessary in the synthesis of choline and acetic acid to form acetylcholine liberated at the neuromuscular junction. This suggests that perhaps the manifestations of essential epilepsy are not entirely cerebral in origin.

Most investigators are of the opinion that enxymes play no part in causation of seizures. Rosenthal (89) stated that as the seizure approaches, there is an increase in blood anti-trypsin, and that following the seizure there is a return to normal. He believed that in epileptic women increased seizures at the menstrual period were due to the premenstrual rise of this enzyme. He suggested that the mechanism of this increase in anti-trypsin activity was the accumulation in the blood of either broken down lipoids from the central nervous system, or possibly intermediary products of albumen splitting, all of which might be regarded as manifestations of an underlying metabolic disturbance. Many corroborated Rosenthal's findings. Wuth (107) summarized all of these findings and concluded that all were erroneous because associated conditions, such as carcinoma, deficiency states, diabetes, and chronic infections were not taken into account, and in these conditions a rise in the anti-tryptic factors always occurred anyway.

FASTING AND THE KETOGENIC DIET

Fasting and the high fat diet have offered a method of treatment especially to children with petit mal manifestations. To date this observation offers a wide field for research into the metabolic etiological factors concerned in essential epilepsy.

The development of the fasting regime for treatment of epilepsy has an interesting history. This material was obtained from an article by Lennox (64) in 1928. Conlin, an osteopathic practitioner, was associated with Bernarr McFadden, a physical culture and diet faddist, who has used the fasting regime for many medical disorders for many years. Dr. Conlin treated a ten year old boy using intermittent periods of fasting and completely cured this patient of his seizures. Since this time Conlin has treated thousands of patients. His explanation for results obtained have been obscure. Indeed, the results he obtained have been obscure. Lennox attempted to get case records on Conlin's numerous patients but failed to obtain an adequate report on these cases. Conlin furnished Lennox and Cobb the case reports of 27 patients, but these records are inadequate because of the absence of information concerning the frequency of seizures before or after the fast, and the length of time which had elapsed since the fast was completed. Conlin reported that his patients' age range was from 13 to 42 years. Seizures were four years' duration or longer. Other therapy had been without benefit. In one-third of the cases there was evidence of a marked decrease in the number of seizures. He added that

he found a decrease in seizures especially in those whom phenobarbital did not affect.

Geyelin (29) in 1921 was impressed by Conlin's apparent success, and reported the treatment before an assembly of skeptical associates. In addition he studied 27 cases for a period of 6 to 20 months. The age of these patients ranged from $2\frac{1}{2}$ to 35 years. Before fasting treatment was begun he looked for abnormal metabolis manifestations in his patients. The shortest duration of seizures in his series was 4 months; the longest, 34 years.. Average duration of seizures was eight years. After the tenth day of the fast, only four out of the 26 had epileptic symptoms. Two showed absence of attacks for one year and 18 showed marked improvement. Six showed no improvement at all.

The results of fasting are well known. The most marked disturbance is increased production of the ketone bodies resulting in loss of base from the body with a subsequent acidotic tendency in the tissue fluids. There is also an associated increase of blood uric acid and a transient hypoglycemia in the early days of the fast. Emphasis has been placed on the acidosis produced, since it is well known that acidosis tends to lower the frequency of all seizures.

Goldbloom (33) in 1922 treated one case of petit mal in a child by the starvation treatment. He completely cured the patient of seizures for a short period of time, after which the patient died of an associated disorder. He suggested that many cases where

success had been reported were possibly hysterical or neuropathic cases. He stressed that organic causes for epilepsy be ruled out completely before evaluating results.

Hoeffel and Moriary (44) in 1924 used two patients for study. They used three fast periods of nine days each. They found an increased excretion of ammonia, and increase in uric acid content of the blood, in addition to a drop in blood sugar and a distinct, but temporary amelioration of symptoms.

Shaw and Moriarty (94) produced a two year study of 19 children showing improvement of symptoms. They attempted standardization of their cases with a preliminary period of 34 days with constant fat, carbohydrate, and protein constituents in the diet under supervised conditions. The duration of the fast was 10 to 14 days. Nothing was given except 75 c.c. of water per kilogram of body weight per day. They found improvement best with large quantities of water. Since many investigators found an increase in blood uric acid after attacks, they attempted to relate this finding with increased uric acid occurring coincident with the fast. This series demonstrated an increase of blood uric acid to 300 per cent over the pre-fasting control in which case attacks did not occur during the fast. They found no correlation. Since they found the usual fall in blood sugar maximum the third to eighth day of fasting, they suggested that the hypoglycemic tendency reported by many in the epileptics had no importance except as a possible protective factor.

Krumpf (79), according to Peterman, in 1924 found the blood sugar rose after reaching a minimum during the fast, glucose synthesis occurring from proteins and fats. In children, however, this synthesis he found not easily accomplished. This, he thought, explained the marked acidotic tendency, and amelioration of symptoms in epileptic children, assuming of course, that acidosis was the factor concerned.

Wilder (105) in 1921, on the basis of Geyelin's results with starvation, first suggested that in diets in which the proportion of carbohydrates and protein was sufficiently restricted might offer a method of treatment of epilepsy, since the basic changes toward ketosis would not be changed, but actually enhanced by a relatively high fat diet. No original explanation of results was given.

Weeks and associates (103) reported a series of cases in 1923. They reviewed the suggestive arguments for a metabolic or chemical disturbance in epilepsy and found that epilepsy resembles other metabolic disorders in that there is absence of organ pathology, there is a progressive course with sequence of aggravation a deterioration, the epileptic tends to be a glutton about food, there is complete or partial relief of symptoms by fasting, and there is a resemblance of human seizures to those of dogs in which pure protein feeding causes convulsions. Weeks also suggested a high fat diet to maintain proper caloric requirements while still maintaining a ketosis. His group studied 73 deteriorated epileptics,

forcing them to take a high fat diet. The most remarkable fact of this study was that the epileptic group tolerated the disagreeable amount of fatty foods. Four thousand and sixty-two calories of fat were given per day, in addition to an adequate protein intake. They found the frequency in seizures seemed to vary accidentally and any decrease in the number of seizures they attributed to psychic influences, not therapeutic.

Peterman (82) in 1924, on the basis of Wilder's suggestion that ketonuria might be of benefit in treatment, treated 86 patients ranging in age from one to fifteen years. He found almost complete cessation of seizures in this group. Since the excretion of acetone bodies was in excess, Perman thought that the high amount of aceto-acetic acid had an anti-convulsant effect. He found best results in petit mal. Peterman (81) reported another series of 37 patients in 1925. The median age was 8 years. He approached Ketosis gradually, by gradual diminution of carbohydrate. He used finally 10 to 15 grams of carbohydrate a day, one gram of protein per kilogram of body weight, and 80 to 90 to 100 grams of fat per day. Vitamins, salts, and free water intake were given. After freedom from attacks from 3 to 4 months, he increased carbohydrate 5 grams per day, every other month, alternating with increase in protein 5 grams per month. Nineteen out of 37 were entirely free from attacks. Eight were free for 2⅓ years. None of his patients had deleterious effects from this type of diet. Attacks were reduced in one case. Peterman thought the effect was

not due to acidosis since administration of sodium bicarbonate did not influence the number of attacks, nor did feeding of intarvin, an odd carbon fat. This seemed to disprove the "acidotic theory."

Talbot and others (98) studied 25 children in 1927 using the ketogenic diet. Since fasting caused increased uric acid, decreased blood sugar, slight acidosis, and a diminished number of seizures, they made corresponding studies with the ketogenic diet. They found that symptomatic cure was present in 30 per cent of their cases. There was not such a marked hypoglycemia nor so high a uric acid level. Feeding excess carbohydrates some time during the ketogenic diet caused diminished ketosis and recurrence of attacks. They made their caloric requirement 50 per cent above the basic level and used 5 grams of fat to one gram of equal parts of carbohydrate and protein.

Kohn, Fries and Felshen (51) determined the relative blood fasting sugar level and glucose tolerance during fasting and during induced ketosis as compared with normal levels. They found that the fasting blood sugar is lowest during starvation and highest during normal periods. During ketosis the fasting level was between the last two levels. During both spontaneous and induced ketosis, the maximum rise of blood sugar is higher than normal, and the fasting level is not reached within three hours. This is merely confirming evidence that the ketogenic diet is as successful as fasting.

What is the essential factor in starvation or induced

ketosis? Wilder and Geyelin attributed it to acidosis, and this was later confirmed by Hoeffel, Moriarty and Shaw. However, as we have already seen, Peterman was first of the opinion that acidosis and ketosis were important factors, but he later showed that it was not entirely due to this condition. Ketosis was maintained even though the urine was made alkaline. Keith and Barrier (48) found that induced chemical acidosis did not diminish the convulsions of epilepsy. They reduced the carbon dioxide combining power to 20 volume %, and the urine pH to 5.4. Peterman (81) already had proved that intarvin replacing fat reduced the acetone bodies in the urine even though the patient still remained free from attacks. Peterman stoutly maintained that it is ketosis and not acidosis which keeps patients seizure-free. All investigators agree that in the ketogenic diet the blood sugar is not so low, acetone bodies are higher, and carbon dioxide combining power is lower than in fasting.

Lennox (60) in 1928 added his word to the subject. He believed beneficial effect was due to the salutary effect of acidosis causing a decrease in the irritability of nerves such as is manifest in muscular cramp, hiccough, or tetany. He believed aceto-acetic acid did not play a sedative role. Lennox found ingestion of acid or acid-forming salts, or a high mixture carbon dioxide inhalation relieved seizures. In regard to the ketogenic diet he believed ingestion of bicarbonate would increase urinary ketones and increase seizures. He further supported his "acidotic theory" by pointing

out that if acidosis has only a salutary effect in relieving seizure frequency in otherwise normal blood, then acidosis should be beneficial in the organic epileptics, which it is. Good results in children, he believed, are due to ready maintenance of ketosis.

Wilkins (106) in 1937 studied 30 children and found 36.6 per cent were free of attacks for long periods of time following the ketogenic diet. Best results were in short standing disease. He was at a loss to know the reasons and suggested it might be only chance.

Using the electro-encephalograph, Jasper and Nichols (47) in 1938 found a decrease in epileptiform activity by use of the ketogenic diet. They considered this a valuable aid in knowing when continuation of therapy was advisable.

Helmholz and Goldstein (40) reported a 15 year study of the ketogenic diet in 1938. They studied 409 patients. Eighty-four were rendered free from attacks for at least one year. One hundred and forty- patients resulted in failure of diminution of attacks. One hundred and forty-two patients were not cooperative. In all, 47 per cent were benefitted. The age of onset was an average of five to ten year group, where 46 per cent remained free after normal diet was instituted again. Also apparent was the fact that more were freed of attacks when the number of attacks was least before treatment. The prognosis was also better in those who were freed from attacks within 20 days of treatment.

Eley (23) in 1933 pointed out the use of the electro-encephalograph as an aid in selection of patients for treatment by means of the ketogenic diet. He also pointed out its prognostic significance. Eley found 33 per cent were improved by the diet and 30 per cent completely cured. Logan (65) and Peterman (78) also believed that the selection of patients should be made with the electro-encephalograph. With the use of this device in the selection of patients he reported a 90 per cent cure (80).

Logan and Baldes (65) also stressed the use of the electro-encephalograph in determining prognosis with the use of the keto - genic diet. Out of 11 cases, eight showed clinical and electro-encephalogram improvement. One case showed clinical without electroencephalogram improgement. Two cases showed no clinical or electro-encephalogram improvement.

The etiological significance of manifestations of the ketogenic diet is at the present time in a state of confusion.

Cholesterol and Lecithin:

These studies are very recent and offer an extremely important challenge to the histologist biochemist. Cholesterol and lecithin are constituents of the cell membrane which many investigators believe important in determining the permeability of the membrane. The importance of this factor is reviewed by Spiegel and Spiegel (96), who state that mechanical, chemical, thermal and electrical stimuli induce excitation by changing the ion concentration on the

semipermeable surface fulms of the cells. These changes in ion concentration act upon the cells by changing the cell membrane permeability. They found anoxemia, alkalosis, and hydration caused a decrease in permiability of the cell membrane. A normally sublinimal stimuli then becomes effective. They suggested epileptogenous agents act by changing the ion concentration of the surface of the nerve cells or by diminution of the density of the cellular surface fulms.

DeCrinis (19) reported a hypercholesteremia in patients with epilepsy. Albertani and Borgatti (2) found hypercholesteremia in dogs during and after the induction of convulsions by the use of camphor and oil, but considered this finding the result of disintegration of brain tissue rather than any specific pathologic state. Pighini (84) found cholesterol in the spinal fluid of epileptic persons, but attributed this to arterial destruction. Campbell (10) in 1925 found the average total blood cholesterol in 124 epileptics to be 148 mg.%, while in 71 normals the average total blood cholesterol was 170 mg.%. Lower levels in epileptics were found within 24 hours of the seizure.

According to Robinson (87), Popea and Vicol (86) in 1925, also found low blood cholesterol, but attributed this to the attack rather than the cause of the attack. They found corresponding lowered cholesterol in normals following exercise. However, in 11 cases he definitely found a lowered cholesterol preceding the seizure.

Robinson, Brain, and Key (87) made a very careful study of 11 patients in 1927. They found a definite hypocholesteremia in 10 out of 11 patients, testing repeatedly both before and after convulsions. They found that the blood cholesterol diminished before attacks and that the attacks occurred at about the lowest levels.

Shope (95) in 1927 found insulin reduced both the blood sugar and blood cholesterol. He noted that fasting causes a corresponding rise in cholesterol, occurring with diminished blood sugar. Shope was of the opinion that the significance of cholesterol in starvation treatment of epilepsy should be further investigated. Lennox, O'Connor, and Bellinger (54) also found a rise in blood cholesterol with fastings.

McQuarrie and associates (70) in 1933 studied the fatty acids and more particularly the lecithin-cholesterol relationships in a group of epileptics as well as in a control group of non-epileptics. They found that in the epileptic group the lecithin was significantly lowered and the total fatty acids significantly higher than in the control group. There was a greater variability in phospholipids and total fatty acids in the epileptic group. There was no constant relationship during the day between seizures and the blood constituents. They found, however, a tendency for the ratio between cholesterol and lecithin to be higher at or near the time of attacks. Strong ketogenic diets were shown to benefit epileptics and such diets also made for a higher level of cholesterol in the blood plasma. Attacks occurred, however, in spite of the elevation.

The number of convulsions was possibly distorted by an attempt to find a relationship between the cholesterol-lecithin ratio rather than any single plasma constituent.

McLean (68) in 1934 demonstrated that dehydration and ketogenesis caused an increase in blood cholesterol and diminution of attacks. He believes the effect is due to the combination of dehydration and increased permeability of the cell membrane due to increased cholesterol content.

Cowie and Magee (15) showed by tissue studies of persons with status epilepticus that the ratio of lecithin to cholesterol was higher than in non-epileptic persons. They also pointed out the fact that the lecithin and cholesterol contents of the cells, particularly the membrane is a constant and a vital factor in cell metabolism.

Aird and Gurchot (1) reviewed the work of Starbenstein and Hendrych (97), who have shown this work of Cowie to be true. They believed, as others, that cholesterol probably diminishes the permeability of the cell membrane while lecithin is credited with the opposite effect. A delicate balance between the two opposed mechanisms is probably essential for cell function.

Cashin and Morvarch (11) in 1927 pointed out that lecithin has a hemolytic effect, an anti-narcotic effect, and attraction of potassium through a cell membrane. Cholesterol has opposite influences on the above mechanisms. Potassium increases the hygroscopic action of lecithin, while cholesterol and calcium retard

it. In addition, the combination of cholesterol and calcium in high concentration has been shown to produce cellular dehydration and shrinkage. Naturally it is,quite apparent that these facts are of major importance to cellular metabolism. Whether lipid variability is causual or casual is then of much etiological importance. It is possible that some other factor is the direct cause, and that abnormality of lipids is merely an associated phenomenon. It is also conceivable that many factors cause a disturbance in the lipid relationships which, when altered, influence epilepsy. That epilepsy may be intimately concerned with the lecithin-cholesterol relationship is suggested by the following observations of McLean (68): "(1) Increased incidence of seizures when the blood cholesterol is high. (2) Evidence that hypocholesteremia or a high lecithin cholesterol ratio accompanies attacks of epilepsy. (3) The beneficial effects of the ketogenic diets and dehydration which have been shown to be associated with an increase in the cholesterol levels of the blood." Similarly, he adds, sedatives and narcotics may be of benefit because of the relative hypercholesteremia they produce.

Aird and Gurchot (1) in 1939 studied the protective effect of high cholesterol against convulsions. They injected cholesterol intravenously into white mice and then attempted to produce convulsions by the injection of coccaine. The cholesterol was given in an organic solvent and before the injection of this substance the diet of the group was carefully controlled and standardized.

Since it had been shown that injection of cholesterol had a sedative effect, as shown by McQuarrie, the question arose as to whether the protection from cholesterol noted in this study might be a direct result of sedation. Airdand Gurchot believed not. They found that the mice could be easily aroused after cholesterol injection, although they did go to sleep immediately afterwards. After the third injection of cholesterol, however, the animals showed no tendency toward drowsiness. They stress that this experiment did not prove that the cell membrane was made less permeable, and so lessened cortical irritability, but did show this might be very likely. Since the control group developed convulsion in 1½ to 3 minutes after injection, and the cholesterol protected group waited 2 to 6 minutes before convulsions began, they presumed that inhibition of absorption of the cocaine into cortical cells had occurred.

These investigators were anxious that their work be repeated. They believed that the semipermeability of the cell membrane is the most important factor in the etiology of epilepsy. They stated, "The psyico-chemical state of cells is dependent on a continuous dynamic equilibrium between the cell and its surrounding medium. The action of cholesterol may be to prevent the adsorption of certain other substances which tend to lower the permeability of the cell membrane to oxygen, resulting in increase in metabolites and subsequent cellular irritation."

SUMMARY

The most definite conclusion that can be arrived at in this review is that the epileptic has a disturbed physiological make-up.

A point that has been stressed in this thesis and which we wish to re-emphasize here is that it must be remembered that the paroxysms of the convulsive reaction reflect physiological changes that are common to normal muscle exertion. Many men failed to take this into account. It explains in part the variety of results and interpretations that are found throughout the literature.

There is no evidence to show that blood sugar plays more than a passive role in the events associated with seizures. Although there is present in the inter-paroxysmal and pre-paroxysmal stages a slight tendency toward decreased blood sugar, there is no proof that the precipitating cause of the seizure is hypoglycemia, or that seizures are in any way etiologically similar to the hypoglycemic convulsions of hyperinsulinism. Glucose tolerance curves have generally shown no abnormality. Results which tend to relate epilepsy to a defective tolerance may in many cases be explained by the motinal make-up of the epileptic. The many endocrine dyscrasias, menstrual disorders, and toxemias all influence the curve and obviously a large group of epileptics are not immune from these disorders. Therefore, it is difficult to prove that a single factor is responsible for any change observed in the sugar level in relation to seizures.

Studies of the protein metabolism in epileptics have been for

the most part negative. It has been reported that non-protein nitrogen, urea nitrogen, amino-acid nitrogen, uric acid, creatinine, ammonia, fibrin, and serum protein values bear no constant relationship either to the degree or duration of epilepsy, nor to the occurrence, time, frequency, or severity of convulsions. Thus far, increased blood fibrinogen appears to be the only direct evidence, according to Goldstein and McFarland (34). Further studies are indicated in significance of increased uric acid in fasting with its associated diminution in seizures. The retention of nitrogen products has been the effect rather than the cause of the seizure. Here again, all of these facts might be due to the effect of physical exertion. The effect of guanadine and guanadine-like substances offer an intriguing theory and an entirely new approach to the problem. Further study is needed.

There appears to be evidence of a disturbed lipoid metabolism in the epileptic. The potentialities in this field are very promising. The fact that there is primarily a disturbance in lipoid metabolism, is related to the reported beneficial effects of the ketogenic diet. The exact nature of this factor is not known. Very important is the fact that, in general, the majority of studies report low blood cholesterol values with a great degree of variability in the same epileptic at different times, or in a group of epileptics at the same time. There is evidence that further studies into cell permeability and the influences of cholesterol and lecithin on this permeability holds great promise in discovering the true

nature of this disease.

In general, criticism of biochemical studies of epileptics have generally been directed to the following points: (1) As a general rule, chronic institutional cases have been used in a majority of studies. The effect of institutional routine, in terms of diet and activity is difficult to evaluate and to control. (2) The difficulty of ascertaining exactly when a seizure is to occur makes it often impossible to obtain blood samples immediately before a seizure. (3) Many seizures occur at night during sleep. (4) Investigators often do not record the time of the seizure or its relation to other seizures.

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