1935

Ketogenic diet in the treatment of epilepsy

W. Riedesel
University of Nebraska Medical Center

THE KETOGENIC DIET IN THE TREATMENT OF EPILEPSY

W. Riedesel

The University of Nebraska College of Medicine

1935

TABLE OF CONTENTS

I. GENERAL STATEMENT

The purpose of this thesis is to present conclusions regarding the ketogenic diet treatment of epilepsy, a phase which is only a small part of the problem of therapy in those disorders included in the syndrome of epilepsy. The whole field of the treatment of epilepsy is too wide and comprehensive to be satisfactorily covered by a thesis such as this one. Therefore, that phase of therapy was chosen which is of special interest because of its chemical and nutritional (metabolic) problems, of its close relationship, experimentally, with the therapy of diabetes mellitus, and because it is the more recent line of attack. The conclusions drawn and the ideas presented herein are based upon what was considered the most representative and authoritative American literature available.

Epilepsy is a symptom, not a disease. The term is from a Greek word meaning "to seize upon" or "a seizure". It consists of the sudden and repeated appearance of seizures, of which disturbances of consciousness, convulsive movements, or both, are the principal element. The term seizure covers various manifestations which patients may exhibit; convulsions, transient losses of consciousness, periods of mental confusion, dreamy states, dizziness, or the performance of automatic acts of which the patient afterwards has no recollection (equivalent with amnesia) are some of the more usual types, but the sympto-

matology is infinitely variable. In general, anypatient who has recurrent seizures is properly called epileptic.

Search for the anatomical locus from which seizures arise has occupied many investigators, but all this localizing is too schematic. Fits or seizures can be set off by disturbances in various parts of the central nervous system. Little is known of the neurological mechanisms involved in an epileptic seizure. There are four theories of the mechanisms listed by Lennox and Cobb (29): (1) The "irritation" theory which arose from the electrical excitation experiments and the pathological findings in Jacksonian epilepsy; (2) the "release" theory suggested by recent advances in physiology, e.g. our newer interpretations of decerebrate rigidity, or of locomotor reflexes. This theory holds that convulsions come not from stimulation, but from a temporary suspension of functions of higher centers which allows the lower centers to discharge explosively; (3) the "short-circuit" theory is obviously allied to the "release" theory, but is more local. A cortical lesion, (for example) is considered capable of interrupting enough association fibers to check the normal spread of nerve impulses and cause them to take a shorter, abnormal route, leading to explosive discharge. The essential difference is that the release theory deals in physiological levels as units, whereas the short circuit conception may be used to explain an epileptic discharge from an anatomical lesion, whether large or small. Lastly, a more general mechanism may be postulated, one that looks on the

neurological pathways involved as incidental. This may be called (4) the "explosive" theory. It holds that a seizure arises as a general widespread change in brain tissue, not dependent on spread of nerve impulses, but upon some sudden metabolic change such as anaphylaxis, anoxemia or alkalosis.

The "explosive" theory, which presumes a sudden alteration of physical or chemical balances throughout the brain substance, offers the largest field for further research.

There are a large number of clinical conditions which may have epileptic seizures as a symptom. Developmental defects, injuries to the central nervous system, infections (encephalitis, meningitis, general paresis), degemerative lesions, convulsant drugs, poisons, excess of insulin, or lack of parathyroid, alterations in circulation,uremia, eclampsia, electric shock, water and oxygen intoxication, acute fever, protein shock, angio-neurotic edema, migrain and emotional shock may be mentioned (35).

It would seem that epilepsy is hereditary in the same manner as other morbid conditions, for example cancer, and diabetes (36, 43, 29). A family history is obtained in only 1/5 of patients because it is not seizures, but the tendency to seizures which is transmitted. The "constitution" or susceptibility is present inall who develop the condition, but whether seizures actually occur may depend on fortuitous contributive causes. The susceptibility may be so strong in one individual that little or no cause is needed to "set-off" an attack, or so weak in another that attacks begin only after

severe stimuli. The most important associated causes are injuries to the central nervous system.

Though gross lesions of the brain occur in most institutional cases, the lesions found are not constant, and may be the result rather than the cause of the seizures. The most common lesions are cortical atrophy, cerebral softening, dilatation of the ventricles, arachnoiditis and gliosis. The frequency or severity of seizures does not parallel the extent of the brain injury.(35) On microscopic examination, areas of degeneration inAmmon's horn are often present. In life, careful neurological examination supplemented by ventriculography may indicate organic lesions in the majority of institutional patients. Convulsions occur in only a small proportion of persons with gross lesions of the brain. Almost any lesion of the brain plus the unknown X which we call functional instability (an inherited tendency), may result in epilepsy. No lesion has been found which is peculiar to persons with seizures, or which is common to all such persons.

Concerning abnormalities in the body elsewhere than in the brain, the most constant is the inconstancy of physiological processes. For example, there is variation from day to day in such measurements as the pH of the blood, oxygen consumption, blood sugar curves, activity of reflexes, vasomotor reactions, leuckocyte counts, excretion of ammonia, weight, and nitrogen balance. (29)

Because no constant structural lesions have been demonstrated in either brains or bodies of persons subject to

seizures, and because in the presence of very obvious abnormalities, such as brain trauma or hypoglycemia, only a minority of patients so affected will have seizures, it is believed that such abnormalities as have been described play only contributory roles. A knowledge of functional abnormalities of nervous tissues is essential for further progress. The greatest recent advance in our knowledge of epilepsy is the demonstration that changes in the physico-chemical processes in the body may definitely modify seizures.

The first of these has to do with acid-base equilibrium. Conditions which produce acidosis - muscular exertion, starvation, ketogenic diet, the breathing of carbon dioxide, and the ingestion of acids or of acid forming salts - tend to reduce seizures, and those causing alkalosis - hyperventilation and ingestion of alkali - tend to increase seizures. McQuarrie and Keith (40) expressed the opinion that the abnormality in acid-base balance observed in certain cases of epilepsy is probably not the factor of chief importance in the mechanism of seizures, but is an incidental accompaniement of a more basic disturbance in the physiology of the nerve cell.

A second condition which modifies seizures is the degree of saturation of the blood with oxygen. Lennox and Cobb (29) have shown that in certain patients having frequent minor attacks, these attacks can be induced by having the patients breathe air which is low in oxygen.

A third consideration is that of water balance. (35, 43,63,21,41,14). Conditions associated with edema of the brain such as eclampsia, nephritis, concussion,alcohol poisoning, or water intoxication induced in animals by forcing fluids are accompanied by convulsions. The opposite effect, dehydration, through a drastic limitation of fluid intake, apparently tends to reduce the number of seizures. Stringent restriction of the total water intake tends to prevent convulsions in many cases of severe epilepsy, even when the patient is on a non-ketogenic diet and is taking no drugs. There is usually an initial loss of weight (water) as in the case of fasting or the use of the ketogenic diet. However, in the majority of severe cases the degree of water restriction (required) for control of seizures is so stringent that continued cooperation on the part of very young patients is almost impossible to obtain without constant supervision. McQuarrie et al (41) report intensive studies of the water and mineral balances made on a severly epileptic girl under experimental conditions in which changes in the state of hydration of the body were induced by various procedures other than water restriction. The establishment of a positive water balance (greater intake than elimination) was regularly followed by convulsive seizures, except one period of intensive phenobarbital therapy. Higher levels of water intake did not seem to favor the occurrence of convulsions so long as active diuresis or catharsis prevented water retention. The results of this study were tentatively interpreted as proving the view that

there is an inherent defect in the mechanism for regulating the semipermeability of the brain cell membrane in certain epileptic subjects. Other observers advocate treatment by sharp curtailment of fluid intake. The regime is said to decrease the number of major, but not of minor, seizures. (35) Although proponents of the dehydration treatment believe that it corrects an underlying defect either in the absorption of fluid from cerebrospinal fluid spaces or in the permeability of nerve cell membranes, there is no proof that it does more than decrease nerve irritability. Closely related to these processes are alterations in certain chemical constituents of the nervous tissues, particularly the electrolytes calcium, sodium, potassium and chloride.

The fact that seizures may be influenced by the different processes mentioned above does not mean that these processes in the epileptic are abnormal. They merely represent conditions under which the epileptic reaction is more easily, or less easily, precipitated. For example, it has not been shown that the nervous tissues of an epileptic are abnormally alkaline or edematous, but only that when alkalosis or edema is induced a seizure mey result. Lennox and Cobb have summarized the physico-chemical changes in the body favoring convulsive reactions as follows: (1) alkalosis, (2) increased cellular permeability, (3) edema, (4) deficient oxygen supply to the nerve cells, (5) high chloride content of tissue fluid, (6 , low calcium. Hopkins (23) showed the average whole-blood

cholesterol values were slightly lower in a group of seven epileptic patients than in a corresponding normal group, and that the cholesterol content of the blood in patients presenting the epileptic syndrome appears to have some significance in indicating the direction in which the physico-chemical changes are taking place since low values occur preparoxysmally in epileptic patients and under conditions of alkalosis. (See Table I)

For that particular type of convulsive disorder which is characterized by its chronicity and by the obscurity of its underlying etiology, the admittedly unsatisfactory term idiopathic epilepsy, for want of a better one, will be employed. Throughout childhood, beyond the sixth year, idiopathic epilepsy is by far the most frequent convulsive seizure. Granting that a small percentage of the patients here classified as idiopathic epileptics might be found by careful encephalographic or postmortem studies to have structural lesions in or about the brain, it is generally conceded that the great majority show no such changes. This, then, brings into numerical prominence the entire class of convulsive disorders for which no definite brain pathology has been demonstrated. (See Chart I). Epileptic seizures above the age of 20 years is only in a small percentage of patients idiopathic.

The therapeutic implications from the foregoing discussion regarding the etiologic factors in idiopathic epilepsy are obvious. However, all practical means of effecting the physiological state of the brain cells are very indirect, a

fact which places a definite limitation on the degree of therapeutic success to be expected.

The central objective in the routine treatment of this disorder in the individual patient is that of preventing seizures and providing, so far as possible, in children, for normal development of his mental and emotional capacities throughout the entire period of growth. Obviously, the immediate aim of all therapy is to remove, or at least alleviate, the causative abnormalities, so far as these can be identified. The encouraging feature is that, although the exact mechanism of seizures is unknown, much can be done to prevent, and in the early stages to relieve them. It is the duty of the physician to search out the various contributing or precipitating factors which, in the individual patient, may make for seizures.

The various aspects of the medical treatment of idiopathic epilepsy are schematically represented in Figure I. The relative importance, which McQuarrie (43) would attach to the various available therapeutic measures is indicated by the size of the sector assigned to each. Long experience has demonstrated that the best plan of therapy is one which simultaneously utilizes all factors known to favor prevention of seizures. Drug therapy for epilepsy, in children, has tended to become less important since the introduction of the dietary regime. Nevertheless, for the vast majority of patients being treated in general practice, special medication still holds a prominent place, if indeed it is not the only type of therapy available. Where possible, drugs should be used merely to supplement the dietary and dehydration forms of management. Phenobarbital is

the most satisfactory single agent so far discovered for control of seizures over long periods of time, and has largely replaced bromides because it does not have the untoward effects of the bromides. In using sedative drugs in epilepsy, care should be taken that more harm than good does not result.

For the sake of the few patients in whom a careful search will produce an etiology that can be corrected, it is essential that every patient showing convulsive seizures be subjected to a thorough working-over. The treatment in each case should include:

(1) For general physical condition, posture, menstruation, thyroid function.

(2) Mental hygiene

(3) Hygiene - general diet therapy

(4) Medication

(5) Special diet therapy.

The effects of the various types of dietetic treatment have been formulated inTable V which shows the points common to the different methods of treatment. The one effect produced by the majority of the types of treatment used,except that of restricting the protein intake, is dehydration of the body tissues. The cause of this change differs,however, with each therapeutic method. Acidosis produces its effect probably by stimulating the action of the kidneys (diuretic) and thus increases the fluid output. During a fast there is reduction of the fluid intake and consequent decrease in the quantity of body fluid. The ketogenic diet so alters the metabolism as to diminish the amount of water in the tissues if the regimen is

prolonged. This is the reverse of what happens with a diet rich in carbohydrate which favors retention of water. Whether the dehydration associated with the ketogenic regimen is the important therapeutic factor, or whether the effectiveness of ketosis is to be ascribed to some unknown or unrecognized factor, has not yet been demonstrated. For clinical purposes it may be assumed the objective of the ketogenic (high fat and low carbohydrate) diet is to cause ketosis.

II

CLINICAL RESULTS AND EXPERIENCES WITH KETOSIS INDUCED BY DIET

It is interesting to note that the use of the Ketogenic diet in epilepsy was the final outcome of a method of treatment or management originally employed by an osteopath, who believed that starvation for a number of days would free the gastro-intestinal tract of unidentified toxic or harmful substances which were held responsible for the seizures. This was first brought to the attention of the medical profession in 1921 by Dr. H. Rawle Geyelin (16) of New York City in a presentation in which he said that two years previously he had had the opportunity to observe the child of a friend who was at the time ten years of age and who had had epilepsy in its most severe form for four years prior to that time. He had had grand mal and petit mal attacks which had become practically continuous. The child had been sent to numerous neurologists and clinicians in the United States and everything had been tried and nothing had succeeded. At Battle Creek, Michigan, he came under the care of Dr. Conklin, an osteopath, who promptly fasted him, the first fast being of fifteen days. This was followed by a period of feeding of three weeks duration and then by a second fast of four or five days. There were four fasting periods over a period of several months. After the second day of fasting the epileptic attacks ceased. Following this Dr. Geyelin had the opportunity to see two other cases treated in the same way by Dr. Conklin, one of which remained

entirely cured for two years, and one for three years. Geyelin himself used fasting as a therapeutic measure with management of epilepsy. In some cases he obtained complete relief over long periods of time; in others, marked improvement; and in a few, no benefit.

Hoeffel and Moriarty (22) report studies of three fasting periods on two cases of epilepsy. It is shown in these studies fasting is accompanied by:

1. A marked reduction of the alkali reserve and a measurable increase in the hydrogen ion concentration of the blood (decreased pH)

2. An increased excretion of ammonia and of the titratable acidity of the urine.

3. A striking increase in the uric acid content of the blood.

4. A decrease in the concentration of the sugar in the blood, which makes a delayed return to normal after the fast is ended.

5. A distinct, but temporary, amelioration of epileptic symptoms.

Shaw and Moriarty (53) showed in a series of five epileptic children that from ten to fourteen day fasts were accompanied by:

1. An increase in uric acid in the blood.

2. Moderately marked acidosis, as indicated by (a)-acetone excretion in the breath, (b) diminished alkali reserve, (c) moderate fall in pH of the plasma.

3. A striking decrease in the blood sugar.

4. A slight diminution in the degree of acidosis and rise in the blood sugar during the latter days of fast. It is suggested by Shaw and Moriarty that the diminution of blood sugar indicates the greater ease of depletion of carbohydrate stores in childhood, and helps to explain the increased tendency to acidosis.

After it was found by chemical examination of the blood and excreta of fasting epileptic patients that ketosis existed whenever the symptoms improved, interest came to center on the ketosis rather than on the intestinal effect of lack of food. Attempts were then made to discover a scientific explanation for the clinical findings. Acetoacetic (or diacetic) acid is produced in starvation as the organism consumes its own substance. Fasting is an effective dehydrating measure and causes ketosis (12).

Fasting is not only a high fat diet, but is also a salt starvation. It has beenobserved frequently that fasting may be more beneficial in epilepsy than the ketogenic diet alone (6). Epileptic patients have unusual ability to consume and utilize fat; and, although there is no definite proof that there is incomplete oxidation of fat, ketosis develops and many patients are definitely improved (2).

Obviously, it is impracticable to attempt to subject patients to repeated periods of fasting in an effort to maintain ketosis. In 1921 R. M. Wilder (61)(60) proposed treating

epilepsy by giving the patient a metabolic mixture (of foods) similar to that found in the fasting state which, when burned in the body would produce diacetic acid, thus avoiding the discomfort and danger of prolonged starvation. At Wilder's suggestion the Pediatric Section at the Mayo Clinic began the use of ketogenic diets, composed largely of fats and with minimal amounts of protein and carbohydrate, in an attempt to supplement or replace the fasting regimen. It was found that the diet would control convulsions in cases in which phenobarbital and other sedatives had failed before (61). It was never supposed that the clinical results to be secured from the ketogenic diet would exceed those obtainable from starvation. The advantage attributed to the diet was that it permitted continuing treatment for months and years.

McQuarrie (40) reports an observation over a period of 41 days on one patient with severe epilepsy, in order to compare the effects (1) of fasting, (2) of a ketogenic diet with a predominant acid ash, (3) of a ketogenic diet with an alkaline ash, and (4) of a non-ketogenic high protein diet with a strongly acid ash, on the occurrence of convulsions. The periods showing the fewest convulsions were those in which the patient fasted or was on a ketogenic diet having an acid ash. The effectiveness of the ketogenic diet was abolished when it was made to have a slightly alkaline ash. With the exception of this alkaline ash period, there was throughout an inverse relationship between the amount of ketone bodies excreted in the

urine and the number of seizures occurring. The non-ketogenic diet with an exceedingly high content of acid forming elements did not have any inhibitory influence whatsoever on the convulsions. McQuarrie and Keith (39) conclude that whatever the explanation of the effect of the ketogenic diet, extensive experience with this form of treatment shows that there is a direct relationship between the degree of improvement and the intensity of the ketosis produced.

Without a preliminary trial it is practically impossible to determine which patients will and which will not respond favorably to dietary treatment. Preliminary encephalographic studies promise to be of assistance in this connection, according to the recent work of Eley (cited by McQuarrie (43) who found that 90% of cases having normal encephalograms responded favorably, while only 12% of those showing abnormalities improved under such treatment. A preliminary fast ofthree or four days duration or longer, with moderate water restriction, is probably the best test. If a patient does not respond to this procedure, it is not likely that he will be greatly benefited by the ketogenic diet.

Hodskins (18) reports he had the best results with what might be called a borderline ketogenic diet; that is, one containing about 120 grams carbohydrate, 60 grams protein, and 155 grams of fat as a daily intake. He says this diet can be taken without hardship, while a "strict ketogenic diet is cumbersome, soon becomes unappetizing, and necessitates altogether

too much discomfort for the amount of good that follows its use". He found it necessary to limit the fluid intake, and also to combine with these two measures the proper individual dose of phenobarbital, sodium bromide, or a combination of the two.

Bassel (4) employs the ketogenic diet in children. He finds that bone and general physical development proceed normally in patients receiving the diet. Two of his patients received a strict diet for more than 18 months and growth was more rapid during that time than inany other period of their development. He advocates combination treatment of diet and phenobarbital which frequently accomplishes what neither will do separately. In cases of adults he treats them by dehydration, luminal and such general restrictions in diet as seems necessary from their histories. Bassel's best results in treatment were seen in children; patients seen early in their history; patients without brain deterioration; and those with grand mal seizures.

Helmholz (21) had treated 369 patients with epilepsy, up until 1932, by means of the ketogenic diet (Tables II and III). Fifty one of these patients had symptomatic epilepsy, forty two were treated for one year or less, and eighty nine did not cooperate sufficiently to judge the effect of the diet. Twenty seven patients could not be included in the group in which treatment was satisfactory for reasons indicated. This leaves a group of 160 on which to judge his results. Of these 36% are well, 21% are improved and 43% were not benefited.

Cooder (12) treated one hundred cases of epilepsy in children up to twelve years of age in a special clinic, with the ketogenic diet with the following results: (three year period)

Total number of patients treated more than 3 months - 38

Patients free of seizures more than 3 months - 19 or 50%

Patients improved - - - - - - - - - - 13 or 34%

Patients not improved - - - - - - - - - 6 or 16%

Ketosis was present for months at a time in his patients without presenting any of the unfavorable symptoms of its related state, acidosis. Often cases on whom CO_2 combining power had been determined, only one showed a low figure (35 volumes %); there was, however, no clinical evidence of acidosis. The patients all soon showed physical improvement, better color, better expression and tissues turgor and other betterments were usually reported by the patients.

His successful patients were roughly divided into three groups: (1) those whose attacks stopped promptly and completely at the commencement of the diet; (2) those whose attacks gradually diminished to zero; and (3) those upon whom the treatment seemed to make no effect until weeks or months later, when their seizures may be suddenly and effectively terminated. It was not possible to foretell what would be the success of any one case. Of the fifty five patients who left the clinic before being discharged, the condtion of forty seven was known: one was said to be free of attacks, a few were improved, but the majority were still having seizures. This

shows that in those who have left treatment there has not been a trend to spontaneous recovery.

Fourteen female and six male patients with idiopathic epilepsy were treated by Natkin(46) in the Manhattan State Hospital with a ketogenic diet for a period of one hundred and eight to seven hundred and twenty nine days, the average duration was three hundred and forty one days. The ages of the patients varied from twenty two to forty seven years. Each patient showed evidence of mental deterioration. The acetone reaction of the urine was positive in 89.5% of the tests taken onthe whole group. With the exception of two cases there was an increase in the number of attacks during the period of the diet. From this we conclude that patients with mental deterioration may respond to the ketogenic diet in a manner quite different from that of patients showing no mental deterioration.

Of fifty six women treated by Barborka (3) with the ketogenic diet, twelve had cessation of menses. This observation calls attention to the possible effect on the hormones of diet high in fat, or perhaps a deficiency in vitamins B and E, that may influence the menstrual cycle. It also brings up the question as to whether the menses will return after resumption of a normal diet. Seven of the twelve returned to normal diet, and normal periods were reëstablished. Later, when brewers' yeast (Vitamin B) was routinely added to the diet, no further trouble of this kind was encountered. Forty seven of the fifty six women were able to do their usual work while on the diet. Only twenty seven of the forty four men were able to do their

usual work while on the diet. This was probably due to the greater physical demands made on the men. Barborka thinks it is not possible because of economic, financial and mental (psychic) reasons to place all patients on a strict diet. For summary of Barborka's results, see Table IV.

The ease of developing and maintaining ketosis and the direct relationship between the degree of improvement and the intensity of ketosis produced differ greatly in different persons, and probably vary in the same person from time to time. In a few cases that have beencontrolled, benefit did not occur until strict ketosis had been maintained for eight months to one year. It is not known whether or not the patient must always maintain a strict ketogenic diet. There is some evidence that a milder degree of ketosis may be sufficient. If the attacks recur when the intensity of ketosis is reduced, a diet should be maintained which produces a degree of ketosis adequate to control the attacks.

The relatively harmless ketosis produced by diet contrasts in sharp contrast with the dangerous ketosis of severe diabetes mellitus. In dieting the lowest point to which the anti-ketogenic glucose falls is about 50 gm. (58% P plus 10% F) (61). This provides a ratio of F.A:G above the threshold of ketosis as we want it, but the excess of ketogenic elements is not large and ill effects from it are negligible. The 50 gm. of antiketone from protein and fat provides adequate protection against ketone coma. (In diabetes every bit of glucose may become unavailable, in which case every gram of fat

stagnates at the ketone stage of its degradation and intoxication is overwhelming.)

The diet, when properly planned, has been taken for years by growing epileptic children with no ill effect. A girl eighteen years old played through a tennis tournament while living on a ketogenic diet and won the tournament without any ill effects. A pellagra-like lesion of the skin occurred among some of the epileptic patients first placed on the ketogenic diet. It apparently was due to the deficiency of vitamin B entailed by the limited amount of greens. It was corrected by feeding yeast preparations.

Radiographs of the long bones of one of twelve children who had been submitted to ketogenic therapy more or less continuously for about two years, were thought by the roentgenologist to reveal abnormally great calcification. This observation lends some support to the warning which Joslin has repeatedly given in regard to the development of arteriosclerosis as a result of prolonged ketosis in diabetes mellitus, although in this child there were no arterial abnormalities (59). Talbot says he does not know of a single instance in which arteriosclerosis has been known to follow ketogenic therapy. Repeated determinations of the blood pressure of the children under his care at the Massachusetts General Hospital failed to reveal evidence of any changes in the arteries. Dr. Joslin says that among 5091 true diabetics whom he has seen there has been no case of epilepsy. Lennox on the other hand, has had two patients suffering from both diabetes and epilepsy.

On the whole the ketogenic diet has proved to be more effective in controlling epileptic seizures in children than in adults. In general, Talbot, found that greater improvement follows establishment of the ketogenic regimen before rather than after puberty. Under suitable control and with the cooperation of the patient,he believes it is equally easy to maintain marked ketosis at all ages. (See Table VI)

Prolonged ketosis does not affect growth and development in any way so long as the fundamental needs of the body are satisfied. (59)(50). If all the food prescribed in the diet is eaten weight can be gained or lost at will by increasing or diminishing the caloric intake. Vitamins are automatically included in abundance, in most diets, for they are present in a majority of the substances given.

A survey of the literature shows a difference in the effect of ketogenic therapy on petit mal and grand mal. In adults, whose common symptom is grandmal, the diet has been relatively unsatisfactory, whereas inchildren it has proved effective. The effectiveness of the ketogenic diet in controling symptomatic epilepsy has been reported in only a few instances. Helmholz states that two out of twelve patients were kept free from attacks for one year or more by this means, and that six were benefited by the treatment. (Cited by Talbot 59).

A decade and a half ago a serious complication was thought to have arisen if acetone bodies appeared in the urine of children with acute illnesses. When, however, the impor-

tance of dehydration in these conditions and the relation of glucose metabolism to ketone formation came to be better understood, the conception of the significance of ketosis changed. It was, nevertheless, with considerable surprise that dietary ketosis was found apparently to act in some way as a protection against disease rather than to constitute a dreaded complication. If a family group includes an individual with dietary ketosis, this individual usually does not develop a common cold to which all are equally exposed, while the other members of the household do become infected. If the subject of ketosis does contract a cold it is usually less severe and of much shorter duration than that of the other members of the family. Peterman (50) reports that five epileptic patients with ketosis recovered normally from severeinfections such as scarlatina, pertussis, and acute respiration infections, although their diets were not altered during the illnesses. From this he concludes that resistance to infection was in no way diminished by ketogenic therapy. It seems justifiable to conclude that continuance of dietary ketosis during intercurrent illness is not harmful. The evidence at hand suggests that the development of ketosis may be a protective reaction of the body during infection and that instead of always being harmful it may at times be beneficial.

During ketogenic therapy the need for the carbohydrate splitting ferments are reduced to a minimum, and the burden of digestion is placed on the fat-splitting ferments

and the bile. Vomiting does not often accompany changes which are made slowly, while it nearly always results when they are too rapid. When a patient vomits it is best to omit one or two meals entirely and allow only water to be taken.

Constipation is almost a constant symptom in epilepsy. As a rule almost every patient is benefited in this respect by ketogenic diet (3,59)

If the need for etherization and operation can be foreseen, it is safer to prepare the patient for the ordeal by building up the carbohydrate reserve for a few hours just as is done in the case of normal individuals. Inso far as has been observed, this in no way alters the favorable course of the dietary treatment.

The first sign that the ketogenic diet is of any benefit is a diminution in the number and severity of seizures. If the patient has been subject to both grand mal and petit mal, the attacks of grand mal usually stop or become less frequent before those of petit mal are markedly affected. Now and then, as soon as ketosis develops all seizures stop.

Another improvement accompanying successful ketogenic therapy is a striking improvement in the personality of the patient, which seems to indicate the so-called "epileptic character" often regarded as causative is but a secondary manifestation of the general condition. After treatment has taken effect the personality of all these patients has undergone a reversal and become quite similar to that of non-epileptic individuals. Talbot mentions one such patient who apparently

did not even know his own name; in two weeks time he not only learned his name, age, address, and the names of his family, but had made a beginning with his A B C's. General physical improvement usually follows dietetic treatment of epilepsy. It soon becomes evident, also, that the skin is clearer, the flesh firmer, the tone of the muscles more clearly normal, and the susceptibility to fatigue greatly diminished. At present it is not possible to determine which patients should and which should not be treated. In general it may be said that treatment can be tried whenever the mentality of the patient is sufficiently good to grasp the methods of dieting, and the courage and will power are great enough to promise persistance. It is a waste of time to treat patients who take liberties with the diet, or who cannot be controlled. The accuracy with which a properly constructed diet is followed can be controlled by the urinary tests for acetone. The patient must be in a suitable environment and have facilities for securing the diet; it is necessary that the patient be willing to spend two or three weeks under direct supervision so that he may learn individually the manner of maintaining and adjusting the ketogenic diet. It is unfair to the patient, at the time he starts treatment to offer him this regimen as a cure. No one can foretell inany individual case whether or not benefit will result.

The type of case of epilepsy which offers the best opportunity for treatment is that of the child or young adult who is just beginning to have seizures, before the convulsive

reaction has become a habit. The type of case in which seizures have been frequent for years with resultant mental deterioration, is of course the least likely to be benefited. Two or three months of the ketogenic diet ordinarily will determine whether or not it is of benefit. In a few instances persisting in the diet has been rewarded by marked improvement finally after several months or a year. Helmholz and Lennox (cited in 34) have treated cases of symptomatic epilepsy and have observed enough improvement to believe that this type may be considered suitable for a trial.

There are a few contraindications to the use of the ketogenic diet. A patient who is already dehydrated by disease is in no condition to tolerate further loss of fluid, and by the same token it is considered unwise to institute dietary ketosis in diabetes mellitus. It also is probably that patients with arteriosclerotic cardiac disease and those with impending cardiac decompensation are not satisfactory subjects.

Factors in failure of the diet in epilepsy are (1) in a majority of cases failure to understand the basic principles of the diet by the patient so that the K:A.K. ratio is upset by minor and unconscious infringments on the diet. Patients frequently use chewing gum, which is sweetened by sugar, unsuspectingly, or take cathartic preparations which also are sweetened; (2) different energy requirements during the course of a day or week necessitating special calculations of the diet; (3) nausea and vomiting by too rapid change from normal low fat to a high fat diet; (4) the difficulty of incorporating large amounts of fat in the diet, since the chief

supply must come from cream, butter, bacon, olive oil and cod liver oil; (5) the sensation of hunger due to lack of bulk in the diet. This can be obviated by the use of bran, agar jelly and gelatin, as fillers; (6) There is a certain monotony in the diet to which patients object; (7) the ketogenic diet is expensive; (8) the sharp limitation of carbohydrates makes the diet unpalatable to many patients; (9) mental deterioration in the patient; (10) failure of attention to the mental hygiene which, as is also the ketogenic diet, is a part of the therapeutic whole.

III. THE CHEMISTRY AND METABOLISM OF KETOSIS

The therapeutic value of fasting in epilepsy led Wilder (61) in 1921 to the thought that a ketone was the factor, in fasting, responsible for inhibiting convulsive seizures. Diacetic acid (CH_3-CO-CH_2COOH) is produced in starvation as the organism consumes its own substance. This compound resembles many of the common anesthetics in its solubility inboth (lipids) and water, as well as its physiological effect. A sedative action is to be expected from compounds of this nature, and it was found, in fact, that the sodium salt of diacetic acid when injected into animals produced a condition of stupor. It was shown by Keith (25)(21) that convulsions of rabbits poisoned with thujone could be inhibited by the sodium salt of certain ketones, and that the inhibition produced by diacetic acid was more effective than that accomplished by related compounds and other sedatives. The effect is less marked than with a similar quantity of phenobarbital, but the latter has a more marked soporific effect. The suggestion has been made by others (chiefly Fay (14) and McQuarrie (41)) that dehydration is the important mechanism of reducing convulsive seizure. Some observers believe the beneficial result of the ketogenic diet in epilepsy is attributable to the dehydration and acidosis that accompany ketosis, but the conditions of the experiments with thujone were not such as to induce dehydration, and since the neutral salt of diacetic was found to be as effective, in preventing

the experimental convulsions, as the free acid, it is clear that the anti-convulsive effect in this instance was owing to something other than acidity.

Ketosis results from abnormal physiological and metabolic processes,. It often occurs during infections, fasting. restriction to high-fat, low-carbohydrate diet, diabetes mellitus, cyclic vomiting and after etherization. It develops when ever there is insufficient carbohydrate available to permit complete combustion or ozidation of fat. Ketosis is not a synonym for acidosis, as many physicians seem to think. The confusion betweenthe terms arose from the earlier descriptions of diabetic coma in which the terms "diabetic ketosis" and "diabetic acidosis", were used rather interchangeably. Ketosis denotes the abnormal production of the three ketone bodies - beta-oxy-butyric acid, diacetic (aceto-acetic) acid, and acetone. Acidosis means either an increase in hydrogen ion concentration (decreased pH) of the blood plasma, or a diminution of the bicarbonate of the blood resulting from accumulation of acid or loss of base. Ketosis is entirely compatible with both a normal serum pH, and a normal bicarbonate reserve, although it usually provokes some degree of acidosis. The two acids unite with available bicarbonate (alkali) of the blood and reduce the ability of the blood to transport carbon dioxide. These acids are excreted, both free and combined as salts, in the urine, while the acetone is eliminated through the urine and breath. At first, both acidosis and ketosis develop but by the end of two or three weeks of ketogenic diet the neutral-

izing mechanisms are brought into play and the acidosis disappears (61).

It is now well established that the three ketone bodies which so far as they are known are the three substances named in the preceding paragraph, have a common origin; two of them are merely products of the third which represents a normal stage in the breakdown of certain other molecules in the body. The first formed of the ketones is diacetic acid, which if it accumulates in the body, is in part reduced to beta-oxy-butyric acid, and in part decarboxylated to become acetone and carbon dioxide.

The theory of Knoop, concerning the method of oxidation of fat, has now received fairly general acceptance. Fatty acids of all kinds, those arising from the hydrolysis of fat, as well as those which result from deaminization of certain amino acids of protein, are attacked by oxidation at their beta carbon atom. The beta carbon atom is the second one from the end carboxyl group as illustrated:

$$-\underset{\delta}{CH_2}-\underset{\gamma}{CH_2}-\overset{*}{\underset{\beta}{CH_2}}-\underset{\alpha}{CH_2}-COOH$$

The long straight chain of the fatty acid is weakened at the point of oxidation, and a split occurs, with loss of the first two carbon atoms. The process is repeated again and again, each time with the loss of two carbon atoms. All the natural fatty acids are straight chains with an <u>even</u> number of carbon atoms. The removal of these carbon atoms leads in every case to butyric acid: $CH_3-CH_2-CH_2-COOH$. Up to this point the completion of each beta-oxidation is independent of accessory

factors, but for reasons which are still obscure, the successive beta-oxidation of the four-carbon chain is dependent on the simultaneous oxidation of glucose. Consequently, under the conditions of the ketogenic diet, as in starvation and likewise in diabetes mellitus, when oxidation of glucose is inadequate, there results incomplete beta oxidation of butyric acid with formation of diacetic acid: CH_3-CO-CH_2-COOH. By reduction this becomes beta oxybutyric acid: CH_3-CHOH-CH_2-COOH, or by decarboxylation, acetone (CH_3-CO-CH_3) and CO_2. This is ketosis. Those substances which are precursors of the ketone bodies are termed ketogenic or ketoplastic (52). Two different classes of food constituents are known to be convertible into diacetic acid: the higher fatty acids of neutral fat, and a few of the amino acids of protein. It is well established that glycerol, the other component of natural fats, is not convertible into ketones, but in the diabetic and probably in the normal subject also, is converted into glucose (52). Similarly the amino acids of protein fall into two classes: (leucin, bucin,) tyrosin, phenylalanine, and possibly histidin and others giving rise to diacetic acid; while glycocol, alanine and others are convertible into glucose. Still other amino-acids as lysine and tryptophane appear to take neither course.

Shaffer (51)(52) worked out the hypothesis that the property possessed by carbohydrate (glucose) and other substances (but chiefly carbohydrates) of preventing the appearance of ketone bodies involved a chemical reaction in which ketogenic substances, mainly fatty acids (fat in the food) were balanced

during normal health by "antiketogenic" substances.(principally carbohydrate). He concluded that one molecule of glucose was antiketogenic (ketolytic) for one molecule of ketogenic substance. Later study seemed to show that in severe ketosis one molecule of glucose is ketolytic for two molecules of fatty acid. The glycerol of fat is a source of antiketogenic material, and abundant enough to affect all accurate computations of the K:A.K. ratio of the diet. Methods of calculating the molecular values of food have been summarized by Shaffer as follows:

A. Ketogenic substance expressed as gram moles of precursors of diacetic acid:

a. 1 gm. fat - $\frac{3 \times 1}{874}$ - 0.00343 mol.

b. 1 gm. urine nitrogen - 0.01 mol.

B. Anti Ketogenic substance expressed as gram-molecular equivalents of glucose:

c. 1 gm. urine nitrogen - $\frac{3.6}{180}$ - 0.020 mol.

d. 1 gm. glucose from carbohydrate - $\frac{1}{180}$ - 0.00556 mol.

e. 1 gm. fat - $\frac{1}{874} \div 2$ - 0.00057 mol.

The formula $\frac{a \text{ plus } b}{c \text{ plus } d \text{ plus } e}$ equals $\frac{K}{AK}$ or

$$5.56 \frac{2.4x \text{ (gms. urinary protein)} + 3.43 \text{ x (gms. fat burned)}}{\text{x (gms.carbohydrate burned)} + 3.2 \text{ x (gms. urinary protein)} + 0.57 \text{ x (gms. fat burned)}}$$

According to Wilder (61)

1 molecule of glucose is equivalent to 2 molecules F.A. (fatty acid)

1 gm. carbohydrate is equivalent to 3 gm. of F.A.

1 gm. food carbohydrate is equivalent to 4 gm. food fat

The (Woodyatt) ratio gm. $\frac{F.A}{gm.G}$ becomes $\frac{3}{1}$ at the threshold of ketogenesis. This ratio becomes about $\frac{2}{1}$ when expressed as $\frac{\text{molecules F A.}}{\text{molecules G}}$ Fatty acids in excess of $\frac{3}{1}$ can be recovered as urinary ketone in almost quantitative proportions, provided always that they actually enter the metabolizing mixture and are not placed in storage. When dogs are made diabetic with phlorhizin and are fed exclusively on meat, they excrete in the urine 3.65 gm. glucose with each 1 gm. of nitrogen. This means that 58% by weight of the dry proteins of the meat have turned to glucose. (1 gm. nitrogen represents about 6.3 gm. protein $\frac{3.65}{6.3}$ x 100 = 58%.) The quota of an A.K. radical in fat glycerol, is 10% of the weight. With substitution of the K:A.K. values foodstuffs according to Woodyatt's description (64): $\frac{K}{AK} - \frac{F.A.}{G.}$, Table VII is obtained:

TABLE VII

Foodstuffs	A.K.%	K.%
Fat	10.00	90
Carbohydrate	100.00	- -
Protein	58.00	46

Talbot, Metcalf and Moriarty (57) have devised an equation, which, although neither mathematically nor scientifically accurate, is far more convenient for general clinical use and involves no errors (larger layer) than those which inevitably arise in computing and weighing out a diet:

$$\frac{K.}{A.K.} = \frac{\text{gms. fat}}{\text{gms. carbohydrate} + \text{gms. protein}} \quad \text{or} \quad \frac{F}{C+P}.$$

See Table VIII for comparisons of calculations of K:A.K.

Ketone formation depends on the food materials in the actual process of being oxidized. This in turn depends on the energy and protein requirements of the organism and is affected insignificantly by the food ingested. Thus, when the diet contains too little protein, the deficit is made good at the expense of the protein taken from the tissues, and if calories are supplied in inadequate number both body fat and protein are consumed. On the other hand, when a diet provides more than is required, the excess escapes oxidation and cannot be considered as a part of the metabolic mixture. A minimum of carbohydrate is indispensable to make the diet palatable at all, and experience has shown that 0.66 gm. protein per kilogram of body weight is necessary to maintain nitrogen (protein) balance in these conditions even when the energy requirements are fully met by fat.

Normally protein is spared whenever possible, and the greater part of the necessary heat (approximately 85%) is derived from fat or carbohydrate. As a source of energy fat can replace carbohydrate only in part. As soon as ketosis develops, the K over AK ratio becomes such that the A.K. content of the protein must be liberated unless carbohydrate can be obtained from an external source. Since traces of the ketones appear in the urine when the K/AK of the food is 2/1 and tests become definite when the ratio is 2.5/1, there is a marked diminution in the protein retention of the body throughout ketogenic therapy (Table IX)

The question of the degree to which fat can replace the protein sparing action of carbohydrate is still under investigation and still unanswered. It seems probable, however, that fat can be successfully substituted for carbohydrate when the total caloric intake is sufficient for maintenance and growth up to the point where it is necessary to utilize the A.K. component of protein, or until the K/AK of the diet is more than 1/1 equals (1). Although the ketone bodies do not appear in detectable amounts (by nitroprusside test) in the urine until the ratio is about 2, it is quite probable that the A.K. factor in protein is called into play before that time.

McQuarrie (39) has shown when the ketogenic diet is given to children during the day, in three or four equal meals, there is a characteristic curve of excretion of the ketone bodies with a high peak in the afternoon and a low level in the early morning hours. As there appears to be a direct relationship between the degree of ketosis and the effectiveness of the diet in preventing epileptic seizures, the wide variations in the degree of ketosis indicated by this curve probably account for many apparent failures in this form of treatment. To be satisfactory, the diet must be so adjusted that the minimal level of ketosis for the day is raised well above the threshold at which seizures occur.

In the children's department of the Massachusetts General Hospital, studies were made by Talbot, Metcalf and Moriarty (9)(57) of the chemical changes which take place in the body during ketogenic therapy and the results were com-

pared with those found during fast, often in the same subjects (see page 13). The changes were found to be almost identical, except that they were less marked during ketogenic dieting than during fast (Figure II). Kohn, Fries, and Felshin (26) performed glucose tolerance tests on nine children before, during and after a ketosis induced by a ketogenic diet:

A. Before the ketosis, normal blood sugar curves were obtained.

B. During the ketosis:

1. The fasting blood-sugar was lower than the normal blood sugar.
2. The maximum rise of the blood-sugar was much higher than the normal and usually delayed. The blood-sugar did not return to the fasting level within three hours, and, therefore, this curve resembled the diabetic sugar curve.

C. After Ketosis:

1. The fasting blood-sugar was lower than normal, but not as low as during ketosis.
2. A normal or high blood sugar was obtained for the first 3-5 days in seven of the cases; for 6 days in one case; and for 8 days in another.
3. A low blood-sugar curve was then obtained which persisted for about eight days. This was characterized by a small maximum rise (about ten to 35 mlgm.) and a rapid return to the fasting

blood sugar level, frequently within one hour, and always within two hours.

The following conclusions were drawn:

1. During ketosis induced by a ketogenic diet, there is a disturbance of carbohydrate metabolism as evidenced by the delayed reaction of the blood sugar following a glucose tolerance test.

2. After the cessation of the ketosis, the carbohydrate metabolism does not return to normal at once, but passes through a transitory stage during which there appears to be an excessive ability to utilize carbohydrate as shown by the occurrence of only a slight rise in the blood sugar following the glucose tolerance test.

3. This low normal blood sugar tolerance curve, following ketosis, may be due to an oversecretion, or increased output of insulin.

Talbot (57) reports the lowest blood sugar concentration found during ketogenic therapy in children was 57 mlgm %, but the figures tended, on the whole, to be above 70 mlgm.%. When the fat content of diet is high, the respiratory quotient (.R.Q.) usually becomes that characteristic of pure fat catabolism: (.70) just as it does during fast.

Gamble, Ross and Tisdall (15) studied the metabolism of the fixed base in the body during fast and obtained evidence of a definite reduction of both body water and plasma bicarbonate which were referable to acetone formation. There was considerable decrease also in the concentration of blood chloride.

When children received ketogenic diets ($2\frac{1}{2}$:1) the intake of both calcium and phosphorus was reduced to approximately $\frac{1}{2}$ and the balance of these salts became negative (Nelson,44). Whether this change is attributable entirely to the reduced intake, as might be expected, or in part to ketosis is difficult to determine. About all that is known definitely is that when the ketogenic diet is used the mineral intake is reduced, the mineral-salt balance is negative, and more calcium and phosphorus are excreted inthe urine than in the feces. The shift of the mineral-salt balance from positive to negative must not be lightly regarded in the management of ketogenic therapy, for under prolonged treatment there might be serious danger of de-mineralization of the body. If the use of the ketogenic diet for a relatively brief period serves to give permanent relief inepilepsy and permits the resumption of a normal diet without recurrence of epileptic seizures, then the negative mineral balance might be disregarded temporarily as being of less importance to the patient than seizures. Whether the metabolism may (itself) adjust itself, to prevent this loss of calcium and phosphorus is yet to be determined. (44).

Whenever the quantity of fluid excreted is greater than the fluid intake, dehydration results. This occurs in a ketogenic (low-carbohydrate) diet. An excessive amount of carbohydrate in the food is believed to increase the body water. The major portion of the decrease in body weight during fasting is due to loss of water. Stark in 1769 (quoted by Lusk) (37) showed that diets high in fat and low in carbohydrate have a

dehydrating effect, and since that time additional evidence has come to light in favor of this observation. Many observers would emphasize this phase of the effects of ketosis especially in its relationship to the physico chemistry of the nervous tissue. It is held that dehydration of the nervous tissue tends to reduce or decrease the irritability of such tissue. Cooder (12) has shown in some twelve to fifteen cases kept in the hospital for a trial period that the diet will produce just as effective dehydration as water restriction. Dehydration is an important underlying cause or result in several forms of treatment and deserves consideration. The loss of weight due to dehydration is abrupt and amounts to from five pounds to ten pounds (2.3 to 4.5 kg.). In most cases it stops in a week, and from then on weight is gradually regained. The symptoms of malaise and discomfort accompanying the institution of the diet are caused by the dehydration, acidosis and the protein breakdown dependent on this acidosis. The protein breakdown is made evident by nitrogen in the urine in excess of that in the food. Acidosis is brought under control by neutralizing mechanisms, chiefly by a mobilization of ammonia in the kidney from urea. (This urea is derived from amino acids of the protein by deaminization in the liver. The resulting acids are then in part converted into ketogenic or in part into antiketogenic material as outlined earlier in this section.)

IV. THE DIETETICS OF INDUCED KETOSIS

It is necessary to discuss some of the factors upon which dietary therapy is based. Various factors must be known whenever dietary therapy is given, particularly to children in whom growth produces special requirements. A child cannot be considered healthy if growth does not progress normally.

There are three periods of life in which the growth impulse is accelerated - during the first six months of infancy; between the ages of five and seven years; and finally, at puberty. (59)

Various features have been suggested as indices of nutrition, but it has become necessary to base judgments upon the relation of weight to height. This ratio is easy to obtain and is a sufficiently accurate index of the developmental and nutritional condition. Individual conditions are rarely identical with average conditions and, within limits, variations from the standard cannot be considered abnormalities. When age is introduced as a third condition in the formation of a standard of growth, many more abnormalities will be revealed than when only weight and height are considered. In practice it is safe to consider malnourished any child ten or more per-cent below the average, and obese any child fifteen or more percent above the average. Special or measured diets for children should supply sufficient food to maintain the body weight at a figure between 3% below and 6% above the average weight considered standard for the patient's height. Since

children are continually growing, when in good health, this standard is continually shifting and should be redetermined at least every four to six months. For adults, the problem of adjustment of diet to bodily requirements is simpler because growth need not be considered. On the whole, it is better for the weight of most adults to be approximately that of the standard or slightly below rather than above it. This is especially true in epileptics, whose tendency to overeat is a well-known symptom.

For no period of life is our knowledge of protein metabolism really satisfactory, but for childhood it is particularly inadequate. It is obvious that throughout life protein consumption must compensate for general wear and tear, and that during childhood it must also provide material for growth. Evidence that the protein requirements of the body are closely related to age even though growth has ceased, is to be found in the fact that the young and healthy adult requires more protein than does the aged adult who is less active. The facts discovered have for the most part been determined by study of the nitrogen elimination in the urine and feces of normal, healthy individuals, and by determination of the quantity of protein needed to establish nitrogen equilibrium within the body. They indicate that in general during infancy, when the food is composed of whole milk, the needs are more than fulfilled by administration of two gms. of protein per kilogram of body weight, and that with a sufficiently large carbohydrate intake, 1.5 gms. per kilogram are probably ade-

quate. During childhood less protein is required than during the first months of life. One gm. per kilogram of body weight usually suffices at this time, - a quantity which provides about 15% of the total calories needed. No absolute standard has yet been obtained for the protein requirements of the adult. (59)

It is desirable to calculate the protein intake not on the basis of the actual weight of the patient but on the basis of the average weight for the age, height and sex in question. This will mean that the obese child receives less than one gm. of protein per kilogram and the thin child more than this amount. Since it is desirable for the obese child to lose weight and for the thin child to gain, this method of determination seems quite logical.

The factor which exerts the most important effect on the retention of protein is the relative proportion of protein, fat and carbohydrate in the diet. Under normal conditions this relationship does not have to be considered but when the food contains a very large proportion of fat and very little carbohydrate as does the ketogenic diet, the interaction of these various foodstuffs in the metabolic process is of great importance. From various studies (59)(58)(3), it has been concluded that when a diet supplying sufficient calories to maintain body weight, contains only minimal amounts of carbohydrate, (8-15 gms.), one gm. of protein per kilogram is usually insufficient to establish and maintain a positive nitrogen balance, because the ketosis taxes the protein molecule for its

antiketogenic fraction. Under such conditions it is probable that a larger protein allowance is necessary. In fifteen children who were undergoing ketogenic therapy at the Massachusetts General Hospital, Dr. Metcalf and Miss Moriarty studied the protein balance (57). In only six out of ninety instances was there evidence of a negative balance when the intake was one gm. per kilogram body weight. Since the output of nitrogen exceeded the intake only when the dietary ratio was 3:1 or 4:1, these investigators concluded that a greater allowance of protein was necessary when the ratio was high. An additional $\frac{1}{4}$ gm. per kilogram appeared to satisfy the extra requirement.

Since about half (58%) of protein is antiketogenic in its action, it is desirable during keto-therapy to reduce the quantity of protein in the food to the minimum compatible with good health in order to permit inclusion in the diet of a small amount of carbohydrate. Without any carbohydrate at all, food is extremely unpalatable. The adequacy of the quantities of protein given each patient should be determined from time to time by examination of the total quantity of urine passed in a period of seventy-two hours. The amount of nitrogen passed in the feces can be disregarded in the dietary calculations, for it is small at most, and decreases as the proportion of fat in the food increases.

According to Mathews (38) "the quantity of protein needed is not independent of the character of the protein, since the amino-acids are the substances which are really

needed, rather than the protein as such. Those proteins which contain all the amino-acids in about the same proportions as they are found in the body are probably more efficient than those which have an excess of one kind or another. Milk and meat protein replace most efficiently the protein consumed."

Since the mineral substances involved in building up the body disintegrate and must be renewed, attention must be paid to the mineral salt content of food, especially when the diet is one-sided. In ordinary diets the supply of sodium, potassium, and magnesium is more than sufficient. The content of calcium, on the other hand, is often inadequate unless special attention is given to the choice of foods. It is estimated by Sherman (54) that the average minimal daily requirement of calcium for an adult weighing seventy kilograms is 0.45 gm. calcium (= 0.63 gm. Ca O). It was found that a normally growing child from three to thirteen years of age needs to absorb not less than one gm. of calcium per day if the rate of storage is to be optimal. During infancy the requirement is 0.17 to 0.18 gm. The best storage results when calcium is supplied in the form of milk, since milk and cream contain more calcium per gm. of carbohydrate than do the vegetables and fruits. (44)

The optimum ration of phosphorus in a mixed diet for a child of eight years was concluded to be 1.58 gm. P205 per day (54). Children three to thirteen years of age, 1.16 - 1.46 gm. per day. Adults, 0.88 gms. phosphorus (2.02 gm. P_2O_5) per day, (per 70 kilogram body weight). Protein has no in-

fluence, but under some conditions carbohydrate increases retention of calcium and phosphorus, and fat diminishes their absorption.

When the diet is restricted in some way for therapeutic purposes, attention to the vitamin content of the food is essential. Particular care is necessary with a diet like that employed for keto-therapy. It should be remembered that a suitable balance is to be maintained between the proportions of the various vitamins in the diet and that never for any length of time should any vitamin be entirely omitted.

Various methods of planning the ketogenic diet are in use by various clinicians. (2,43,57,44,61,4,59,47,48(Some have developed simplified, approximate calculations so that the patient or one of his family will be able to calculate and prepare his own menus without further assistance and with assurance of success, after a short period of instruction and demonstration. Barborka says (2): "Two conditions are necessary to the utilization of the ketogenic diet; a simple method of calculating it, and education of the patient in the construction of diets from the calculation." The process is the same as that in the instance of a diabetic patient.

All authorities agree that the calculation of the ketogenic diet depends on two principles: the total amount of food given must correspond as closely as possible with the total energy requirements of the patient. If the diet happens to match exactly the body's consuption of carbohydrate, protein and fat from exogenous and endogenous sources, the calories

contained in the diet will be utilized each day in metabolism without either storing up excess or drawing from the patient's own stores; Second, ketosis shown by positive test for acetone and diacetic acid in the urine, must be developed and maintained. It has been found that a reduction or cessation of the epileptic attacks can not be expected until the diet is sufficient to produce a marked ketosis. (57)

In the ketogenic diet the ketogenic factors overbalance the antiketogenic factors in the food ingested. The diet consists of a large amount of fat and minimal amount of protein and carbohydrate, so that inadequate amounts of glucose are available to assist the oxidation of fatty acids, and the intermediate oxidation products, diacetic acid, betaoxybutyric acid and acetone, are formed in excess and accumulate in the tissues. Ratios of F.A/G (fatty acids to glucose) of 2:1; 3:1; 4:1 are commonly employed to produce mild ketosis. (Ratios expressed in grams.)

The total caloric requirement, as has been often emphasized in the literature, will depend on the height, weight and physical characteristics of the patient, as well as the mode of life. In epileptic children normal activity is encouraged, but it has seemed best not to have them undergo severe muscular strain, and over-fatigue is guarded against. With this inview, the total calories in the diet given must be sufficient not only to maintain the body weight, with normal activity, but also to allow a surplus for growth.

The total caloric needs should be based upon the normal weight of the child for its height. (Table X) 50% should be added to the basal needs to allow for exercise, growth and loss in excreta. It has been found that the children who received their basal requirement (based on Du Bois standards) plus 50%, with rare exceptions, gained weight in a normal manner. This made it clear that their total caloric requirements were being supplied. These are minimal needs. The maximal basal requirements are less readily determined. Over-eating is just as bad, if not worse, for the health of an epileptic child than is under-eating. In practice it is generally wise to give at first a little more than the minimal caloric requirement and to weigh the child once a week to determine whether or not this is sufficient.

With the development of ketosis and the increased excretion of bases, some loss of weight may be expected because of the accompanying dehydration. If, after the diet is found which produces adequate ketosis, the patient's weight does not remain reasonably constant, the calories are raised or lowered depending on whether there has been a gain or loss in weight. If, for any reason, the total energy demands are lessened, it is necessary to reduce correspondingly the total calories of the diet and to recalculate the quantity of fat, carbohydrate and protein on the new basis.

Deficiency of calories may defeat the purpose by causing excessive destruction of tissue protein, thus adding sugar to the metabolic mixture and disturbing the K:A.K. ratio.

Practical Management

Patients or their guardians must be carefully and systematically trained for the ketogenic therapy. While the diet is being adjusted the patient is learning how to use scales, how to use food tables, and how to translate the diet prescription, which calls for grams of carbohydrate, fat and protein, into meals and into terms of vegetables, eggs, and other foodstuffs. He is also instructed how to test the urine for diacetic acid (Gerhart's test: "Use two small test tubes, such as those used in the Wassermann test. Add to one tube 1 cc. of water and 1 cc. of 10% aqueous solution of ferric chloride and mix. Add to the other tube 1 cc. of urine and 1 cc. of ferric chloride solution and mix. If the tube containing the urine is darker than the control tube, diacetic acid is present. Caution: the patient must not have been using acetylsalicytic acid, or other phenol derivatives, as medicine". (61)

The patient should be warned against foods of unknown composition, toothpaste, cough syrups, sweetened laxatives, and chewing gum.

The prime requisite for the clinical management of epilepsy by keto-therapy is a knowledge of the amount of fat. carbohydrate and protein in the various foods commonly used. (See Table XVI)

Wilder and Pollock (61) emphasize that the calories be calculated with the greatest accuracy. The principal foods which they allow are butter, eggs, meat and cream (40% butter

fat). They include 50 to 80 gm. of tomatoes every other day as a source of vitamin C, together with 50 or 100 gm.of other vegetables or fruit with carbohydrate content of less than 5%. The only bread they allow is gluten bread produced by The Loeb Dietetic Food Company of NewYork City, of which one thin slice adds not more than the equivalent of one gm. of glucose tothe diet.

Barborka has prepared tables for the use of the clinician and patient which simplify calculations. (Tables XI - XIV) They are not exact from the standpoint of theoretic relationships involved but are sufficiently accurate for clinical work. The resulting diets conform to the theory of ketosis as developed by Woodyatt and Shaffer. Before patients are given the ketogenic diet, their total calories for twenty-four hours must be estimated. For practical purposes Barborka considers the energy requirement for the ordinary adult patient is approximately sixteen calories for each pound of body weight (35 calories per kilogram) and for the ordinary child. twenty-five calories for each pound (54.5 calories per kilogram). The carbohydrates, fat and protein are then calculatted according to diet one (in Table XI) This diet is continued for three to four days. There will be little difficulty with vomiting and nausea if the change from normal diet to ketogenic diet is made gradually. If nausea does occur small amounts of orange juice may be prescribed. For several days intermediate diets as diet two, or a short fasting period for one or two days, may be interposed before instituting diets higher in fat

(Diet 3). Diet 3 can be continued for 3 to 5 days, as a result of which Ketosis usually begins. Diets 4, 5, and 6 are then given in order to intensify the ketosis of this is necessary to control the attacks. Diet 1 may be continued for one week as a test diet to determine whether or not the total estimated calories are sufficient for the maintenance of body weight, allowing a fluctuation of one or two pounds gain or loss. If the weight does not remain reasonably constant the calories are raised or lowered as indicated.

Theoretical considerations involved may be ignored and the amount of carbohydrate in grams calculated by multiplying the total calories by 0.035 to 0.006 (see Table of Diets) Thus, carbohydrate is a certain percentage (3.5% to 0.6%) of the total calories. The protein quota is calculated as one third of the body weight in pounds (or two thirds the weight in kilograms). The fat quota is obtained by multiplying the total calories by 0.09 or 0.10.

Because of a possible lack of vitamin B in the diet, Barborka incorporates as a routine, one half to one teaspoonful of Brewer's yeast daily. Since there is a negative balance of calcium, small doses of calcium lactate or of calcium phosphate are given.

Lennox and Cobb give one or two gms. protein per kilogram of body weight, a ratio of two,three or four gms. of fat to one gm. of combined protein and carbohydrate, with total calories sufficient to nearly maintain the patient's usual weight. (35) The patients should have the urine examined daily

for diacetic acid or acetone.

Talbot (59), assuming the normal diet contains one part of ketogenic material to every four to six parts of non-ketogenic material, begins therapy by changing the K:A.K. ratio to $1\frac{1}{2}$:1. After two or three weeks of this ratio, further changes are made at intervals of one week to the ratios: 2:1, 2.5:1, 3:1, 3.5:1 and, if necessary, 4,or more :1. "It should be kept in mind, throughout these changes, however, that in no case, is the daily carbohydrate content of the diet to be reduced below eight gms." For sake of simplicity, the K:A.K. ratio is expressed in terms of grams of food rather than in molecular-gram values.

He further states it is unwise to change suddenly from a strong ketogenic diet to a normal one. If the time has come to return to a normal or nearly normal diet, the best proceedure is either to add ten gms. of carbohydrate and omit 4.5 gms. of fat, progressively at two-week intervals, or to change the K:A.K. ratio every three or four weeks in the sequence 4:1, $3\frac{1}{2}$:1, 3:1, $2\frac{1}{2}$:1, 2:1, $1\frac{1}{2}$:1. He advises this last ratio should preferably be maintained for a month or two before the patient receives a less restricted, normal assortment of foods. Should epileptic symptoms appear after a period of freedom from dietary restrictions, the ratio may be increased very rapidly, so that at the end of two weeks it has reached the maximum ever previously used.

Talbot (59) uses the method of Metcalf and Moriarty (57) to calculate the K:A.K. ratio. Their formula is:

Total calories = Ratio x 9(C+P) + 4C + 4P

He uses the following illustrative case as an example: To estimate a diet with a 2.5:1 ratio for a child nine years old. The patient is a normal quiet girl nine years old, 51 inches tall, who weighs 61½ pounds (28 kgm.). See Table X. Since the minimum needs are 1375 and the maximum 2300 calories, the therapeutic diet should contain 1600 calories or about 200 more than the minimal allowance. Had the patient been active, 1800 calories would have been a better number for the initial quota. (In this case it is assumed that 1600 calories is adequate provision, because the child presumably has been watched while receiving suitable diets with the ratios 1½:1 and 2:1) The problem here is to calculate the relative amounts of the carbohydrate, protein and fat which will produce a K:A.K. of 2½:1. The quantity of protein to be given is determined by the body weight of the patient: 1 gm. per kilogram of body weight is minimal. This allowance of 28 gms. is increased by 3 gms. (10%) to compensate for the extra loss of protein which accompanies ketosis and a decrease in carbohydrate intake.

First is used the formula:

(1) $\frac{K}{A.K.} = \frac{F}{C+P}$ (see page 33) This becomes:

(2) $\frac{2.5}{1} = \frac{F}{C+31}$

(3) $F = 2.5(C+31)$

If F, C, and P represent grams of fat, carbohydrate and protein respectively which are needed in the diet, and if it is known that 1 gm.F. = 9 calories; 1 gm.P = 4 calories; and 1 gm.C =

4 calories, we can use the formula:

(4) $1600 = 9F + 4C + 4P$ Substituting known values for fat (from B) and protein, we have:

(5) $1600 = 9(2.5\ (C-31)) + 4C + 4(31)$

(6) $1600 = 9(2.5C + 77.5) + 4C + 124$

(7) $1600 = 22.5C + 697.5 + 4C + 124$

(8) $1600 = 26.5C + 821.5$

(9) $26.5C = 1600 - 821.5 = 778.5$

(10) $\underline{C} = \frac{778.5}{25.4} = \underline{29.4 \text{ gms.}}$

(11) $P = 31 \times 4 = 124$ calories

$C = 29.4 \times 4 = \frac{117.6}{231.6}$ calories

(12) $9F = 1600 - 231.6$ calories $= 1368.4$ calories

$\underline{F} = \frac{1368.4}{9} = \underline{152.0 \text{ gms.}}$

(Dr. Eliot Luther and Dr. Walter Bartlett of the Massachusetts General Hospital have calculated all the results necessary and compiled them in a table (Table XXIV p.224 "Treatment of Epilepsy" by Talbot.))

Each meal is to contain one-third of this daily allowance so that its K:A.K. shall be identical with that of the diet as a whole. Therefore, in each meal there will be $\frac{31}{3}$ = 10 gms.P; $\frac{27}{3}$ = 9 gms.C; and $\frac{152}{3}$ = 51 gms.F.

Bread is entirely to be replaced by specially prepared bran wafers (or Loeb's Gluten Bread, one slice = 1 gm.G). If necessary food may be sweetened with saccharin, never with sugar. The sugar-less, food-free gelatine substance D'Zerta constitutes a fairly satisfactory substitute for desserts.

It provides a pleasant medium for the cream necessarily included in the menu, for just like any other gelatine dessert, it may be served with whipped cream flavored with vanilla if desired. If an egg is to be fried, mineral oil must be used in the pan, for there is no practical means of measuring the amount of fat absorbed during cooking. To allay the discomforts which result from undue concentration of food, care must be exercised to supply sufficient bulky matter in the diet. This will do away with a constant sense of hunger, and will tend to prevent constipation. Meats are to be weighed after cooking, and must not be cooked with sauces of any kind. Care must be taken to ascertain that only lean meat is included in the material weighed.

As a routine to prevent constipation, Talbot requires all epileptics to take one dose of Karlsbad salts weekly.

Bassel (4) uses viosteral as well as brewer's yeast as a precaution against any deficiency disease. He restricts fluids to as nearly three pints daily as possible. If the time for observationtherapy is limited, he fasts the patient for twenty-four hours and ketosis is produced sooner. His patients remain in ketosis for six to twenty weeks, and then gradually resume a normal diet. In some patients, in whom the attacks return, the diet is continued indefinitely.

McQuarrie (43) employs the ketogenic diet, believing its dehydrating effect is of prime importance, but emphasizes that more satisfactory results are accomplished by utilizing all appropriate dietary principles rather than any single

regimen alone. He says a preliminary fast of severals days duration is often desirable. moderate restriction of the total water and salt intake in conjunction with the ketogenic diet permits a more liberal allowance of carbohydrate, while use of a mildly ketogenic or border-line diet in connection with the low-water exhange regimen makes the degree of water restriction required for control of seizures less extreme and so more tolerable to the patient. No exact rule regarding the amount of water to be allowed can be laid down for application in all cases, because the requirements vary so widely for different conditions, such as age,muscular activity, and atmospheric conditions. After seizures have been brought under control, sufficient water must be given with the diet to meet all the physiological requirements, including the process of growth, with unimpaired efficiency. McQuarrie employs an incomplete substitute for sweet milk, which he says cannot be given in adequate amounts. This substitute is made by adding 3.5 gm. of casein powder (Casic) and 46 gm. of water to 50 gms. of heavy cream, and seasoning the mixture with saccharin and salt. McQuarrie further states that since the purpose of the ketogenic diet can be defeated by the presence of a fixed base, it has been desirable to omit baking soda and other alkalies, and to select dietary constituents, so far as possible, whose metabolic end products are predominantly acid. Practically all fruits and vegetables, excepting cereal grains, have an alkaline ash, while the latter and all proteins have an acid ash. Because it is desirable to include as much fresh vegetable food

in the diet as the carbohydrate and water allowances will permit, it is occasionally found helpful in severe cases to supplement the diet with the quantity of weak H Cl, or of acid-forming salts (such as ammonium or calcium chloride) necessary to neutralize the excess alkali occurring in the vegetable constituents. These may practically be used as substitutes for vinegar in salad dressing, and for table salt. The combined regimen is most likely to be effective when the specific gravity of the urine ranges above 1.028.

The constituents of the diet should be carefully weighed, especially at the beginning of treatment, and until they can be fairly accurately estimated.

To simplify calculation of the ketogenic, low-water diet according to the total caloric, protein and water requirements for children of different ages and weights, McQuarrie uses the general guide shown in table XV. All that is required for its use are knowledge of the patient's age and weight, and a standard table of food values. The factor by which the body weight is multipliedin the equation for estimating fat, is one derived more or less empirically from average figures for caloric requirements of children under conditions of moderate activity. Variations in its value for different ages or weights involve assumed differences in protein and carbohydrate, as well as caloric requirements. Diets calculated according to this guide should provide a metabolic mixture having a ratio K:A.K. of approximately 3:1. Most of the foods suitable for this type of diet are given in Table XVI. The values as tested

are for uncookedfoods. Baking causes a loss of from 20 - 30% in the water content for meats and vegetables.

V. SUMMARY

Epilepsy is a symptom, not a disease. Two forms are clinically recognized, but the distinction between the two is not sharp. Symptomatic epilepsy has a demonstrable organic cause, while idiopathic epilepsy is apparently without organic cause, so far as can be demonstrated during life or after death. Idiopathic epilepsy occurs more frequently in early childhood, when it constitutes the greater part of all convulsive seizures, or may be delayed in onset until young adult life. After twenty years of age, organic causes of convulsive seizures are more frequently demonstrated.

There is no characteristic organic lesion which is held as etiologic. Within the past twenty years more emphasis is being placed upon functional changes occurring in the nervous system as a result of alteration in the physico-chemical balance of nerve tissues.

In 1921 Geyelin brought to the attention of the medical profession the successful control of convulsive seizures by fasting as practiced by Conklin, an osteopathic physician. Wilder, believing that the ketone bodies, which were constantly present in the urine of fasting ptients, exerted a sedative effect on the nervous tissue, suggested the artificial induction of ketosis by dietary regulation, as a therapeutic regimen. The ability of clinicians to produce an induced state of ketosis by a calculated high-fat, low-carbohydrate diet was made possible through the chemical investigations by several biochemists and physiologists, of the abnormal metabolism of

of patients with diabetes mellitus. Wilder, Woodyatt, Shaffer have been leaders in this field in the experimental phase. It has been demonstrated that the metabolic oxidation of fatty acids, of even numbered carbon atoms, leads to an intermediate product butyric acid. The final oxidation to carbondioxide and water is accomplished only by the simultaneous oxidation of one molecule of glucose to every one or two molecules of butyric acid. When inadequate glucose is available, the butyric acid becomes converted into diacetic acid. By reduction, this becomes beta-oxybutyric acid, and by decarboxylation acetone and CO_2. Woodyatt has shown that 90% of fat and 46% of protein produce fatty acids - they are ketogenic material; and that 10% of fat, 58% of protein and 100% of carbohydrate produce glucose in the body and they are anti-ketogenic. On the basis of this analysis, or a more elaborate gram molecular relationship established by Shaffer, simple methods of calculating diets to produce ketosis have been worked out and applied by clinicians (Wilder, Barborka, McQuarrie, Talbot and Metcalf, etc.)

The whole mechanism of why ketosis inhibits the occurrence of convulsive seizures is not understood. McQuarrie and Fay place special emphasis on the dehydrating effect; others emphasize the alteration of the acid-base balance toward the acid side.

Clinical applications of induced ketosis have been made by Peterman, Helmholz, Keith, Barborka, Lennox, Cobb, Talbot, Metcalf, Bridge and Job, McQuarrie and Cooder. What ever explanation of the mechanism of the ketogenic diet may

finally prove correct, most persons who have had experience with this form of therapy now agree that there is a direct relationship between the degree of improvement and the intensity of the ketosis produced.

Certain physiological changes which take place in the blood chemistry during restriction to a ketogenic diet are the same as those which accompany fasting. Careful investigations have shown the sugar content of the blood is low, acetone bodies are present in increasedquantities in both the breath and urine, the CO_2 combining power of the blood is diminished and the pH of the blood is slightly reduced. The quantity of the N.P.N. or amino acids in the blood remain within normal limits. There is a negative balance of calcium and phosphorus, and of water. These effects are supposed, theoretically, to lower nervous excitability, by their combined effect on cell membrane permeability.

The diet must be exact and adjusted for each person to meet his particular requirements as regards: (a) the necessary degree of ketosis to prevent attacks, (b) total caloric value for energy requirements including growth in children, (c) protein(balance) vitamin, mineral salt requirements, and (d) digestibility and taste. A preliminary fast of a few days tends to insure the success of the ketogenic diet.

The ketogenic diet has been in use for over ten years and it may fairly be said to be the most valuable single therapeutic measure in the present list for the treatment of idiopathic epilepsy. It has afforded ten year cures in from 30 -

36% of cases observed by Geyelin and Helmholz, and improvement ina larger percentage. The superiority of the diet is not only becauseof its greater effectiveness, but because it can be continuously maintained for an indefinite period while some of the other forms of treatment can not be. No unfavorable results are observed due directly to the effects of ketosis except in a rare diabetic patient, or one who is already much dehydrated. Growth and physical and mental development are faorably influenced. Observers have noted improvement in the physical condition of patients under keto therapy. Patients with marked mental deterioration show a poor response to keto-therapy, and for them it is not recommended.

The best results in treatment are seen in:

1. Children,
2. Patients seen early in their history of seizures,
3. Patients without mental deterioration,
4, Those with grand mal seizures,
5. The idiopathic form,
6. Patients who cooperate well with the regimen.

BIBLIOGRAPHY

1. Barborka, C.J.; "The Ketogenic Diet Treatment of Epilepsy in Adults" Journal A.M.A. 91:73 (1928)

2. Barborka, C.J.; "The Ketogenic Diet and Its Uses" Medical Clinics of North America 12:1639 (1929)

3. Barborka, C.J.; "The Results of Treatment by Ketogenic Diet in One Hundred Cases of Epilepsy in Adults" Archives of Neurology and Psychiatry 23:904 (1930)

4. Bassel, P.M.; "Epileptic Syndrome and Treatment" Texas State Journal of Medicine 29:736 (1934)

5. Brain, W.R.; "Inheritance of Epilepsy" Quarterly Journal of Medicine 19:299 (1926)

6. Bridge, M., and Job, L.V.; "Mechanism of Ketogenic Diets in Epilepsy" American Journal of Psychiatry 10:667 (1931)

7. Campbell, C.M.; "On the Mechanism of Convulsive Phenomena and Allied Symptoms" Bulletin Johns Hopkins Hospital 28:318 (1917)

8. Campbell, C.M.; "Tissue Oxygen Tension with Special Refernce to Tetany and Convulsions" Journal of Physiology 60:347 (1925)

9. Clark, L.P.; "Dietetic Treatment of Epileptics" Boston Medical and Surgical Journal 195:311 (1926b)

10. Cobb, S.; "A Case of Epilepsy with a General Discussion of the Pathology" Medical Clinics of North America 5:1404 (1922)

11. Cobb, S.; "Causes of Epilepsy" Archives of Neurology and Psychiatry 27: 1245 (1932)

12. Cooder, H.R.; "Epilepsy in Children with Particular Reference to the Ketogenic Diet" California & Western Medicine 39:169 (1933)

13. Elsberg, C.A., and Stookey, B.P.; "Studies on Epilepsy. Convulsions Experimentally Produced in Animals Compared with Convulsive States in Man" Archives of Neurology and Psychiatry 9:613 (1923)

14. Fay, Temple; "Some Factors in the 'Mechanical Theory' of Epilepsy, with Special Reference to the Influence of Fluid and its Control in the Treatment of Certain Cases" American Journal of Psychiatry 8:783 (1929)

15. Gamble, J.L., Ross, G.S., and Tisdall, F.F.; "The Metabolism of Fixed Base During Fasting" Journal of Biological Chemistry 57:633 (1927)

BIBLIOGRAPH

16. Geyelin, H.R.; "Fasting as a Method for Treating Epilepsy" Medical Record of New York 99:1037 (1921)

17. Goldbloom, A.; "Some Observations on the Starvation Treatment of Epilepsy" Canadian Medical Association Journal 12:539 (1922)

18. Hodskins, M.D.; "The Treatment of Epilepsy" Journal of Nervous and Mental Diseases" 77:502 (1933)

19. Helmholz, H.F., and Keith, H.M.; "Treatment of Epilepsy in Childhood" Journal A.M.A. 88:2027 (1927)

20. Helmholz, H.F., and Keith, H.M.; "Eight Years Experience in the Treatment of Epilepsy" Journal A.M.A. 95:707 (1930)

21. Helmholz, H.F. and Keith, H.M.; "Ten Years Experience in the Treatment of Epilepsy" Collected Papers of the Mayo Clinic 25:1082 (1932)

22. Hoeffel, G.N., and Moriarty, M.E.; "The Effect of Fasting on the Metabolism of Epileptic Children" American Journal of the Diseases of Children 28:16 (1924)

23. Hopkins, Helen; "Chemical Studies in the Epileptic Syndrome" Journal of Nervous and Mental Diseases 7:601 (1933)

24. Inskeep, L.D.; "Idiopathic Epilepsy; Etiologic Factors" Northwest Medicine 32:248 (1933)

25. Keith, H.M.; "Various Factors in Experimental Convulsions" American Journal Diseases Children 41:532 (1931)

26. Kohn, J.L., Fries, M.E., Felshin, G.; "Spontaneous and Indirect Ketosis in Children" American Jour. of Diseases of Children 34:857 (1921)

27. Lennox, W.G., O'Connor, W.F., and Bellinger, M.; "Chemical Changes in Blood During Fasting in the Human Subject" Archives of Internal Medicine 38:553 (1926)

28. Lennox, W.G.; "The Effect on Epileptic Seizures of Altering the Acid Base Relationship of the Blood" Journal of Clinical Investigation 4:429 (1927)

29. Lennox, W.G., and Cobb, S.; "Epilepsy from Point of View of Physiology and Treatment" Medicine 7:105 (1928)

30. Lennox, W.G., and Bellinger, M.; "Repeated Blood Sugar Curves in Non-Diabetic Subjects" Journal of Clinical Investigation 4:331 (1927)

BIBLIOGRAPHY

31. Lennox, W.G.; "Multiple Causes of Seizures in Patients" New England Journal of Medicine 209:386 (1933)

32. Lennox, W.G. and Allen, M.; "Studies in the Metabolism of Epilepsy: IV The Plasma Bicarbonate." Archives of Neurology and Psychiatry 20:155 (1928)

33. Lennox, W.G. and Cobb, S.; "Studies in the Metabolism of Epilepsy: VI. The Clinical Effect of Fasting" Archives of Neurology and Psychiatry 20:771 (1928)

34. Lennox, W.G. and Cobb, S.; "Epilepsy" Nelson's Loose-Leaf System of Medicine Vol.VI (1933) Thomas Nelson and Sons

35. Lennox, W.G. and Cobb, S.; "Epilepsy" Oxford Medicine Vol.VI part II p.893

36. Lennox, W.G.; "A View of Epilepsy after 10 years of Research" Journal Nervous and Mental Diseases 77:504 (1933)

37. Lusk, G.; "The Elements of the Science of Nutrition" W.B.Saunders, Philadelphia (1928) 4th Edition

38. Mathews, A.P.; "Physiological Chemistry. A textbook and manual for Students" Wm. Wood & Company, N. Y. 19

39. McQuarrie, I.; and Keith, H.M.; "The Relationship of Variations in the degree of Ketonuria to Occurences of Convulsions in Epileptic Children on Ketogenic Diets" American Journal of the Diseases of Children. 34:1013 (1927)

40. McQuarrie, I., and Keith, H.M.; "Experimental Study of the Acid-Base Equilibrium in Children with Idiopathic Epilepsy" American Journal of Diseases of Children 37:261 (1929)

41. McQuarrie, I., Manchester, R.C., and Husted, C.; "Study of Water and Mineral Balance in Epileptic Children: I Effect of Diuresis, Catharsis, Phenobarbital Therapy and Water Storage" American Journal of the Diseases of Children 43:1519 (1932)

42. McQuarrie, I., Husted, C., and Bloor, W.R.; "The Lipids of the Blood Plasma in Epilepsy" Journal of Clinical Investigation 12:255 (1933)

43. McQuarrie, I.; "Non-organic Convulsive Disorders of Childhood with Special Reference to Idiopathic Epilepsy" California and Western Medicine 41:1:1 and 41:2:86 (1934)

BIBLIOGRAPHY

44. Nelson, M. van K.; "Calcium and Phosphorus Metabolism of Epileptic Children Receiving a Ketogenic Diet" American Journal of Diseases of Children 36:716 (1928)

45. Notkin, J.; "Treatment of Institutionalized Adult Patients with the Ketogenic Diet" Archives of Neurology and Psychiatry 31:787 (1934)

46. Notkin, J.; "A Report of the Treatment of Institutionalized Adult Epileptic Patients with the Ketogenic Diet" Journal of Nervous and Mental Diseases 79:434 (1934)

47. Peterman, M.G.; "Treatment of Epilepsy in Childhood" Chapter LVII Supplement of "Billings-Forschheimer's Therapeusis of Internal Diseases"

48. Peterman, M.G.; "The Ketogenic Diet in the Treatment of Epilepsy" American Journal Diseases of Children 28:28 (1924)

49. Peterman, M.G.; "The Ketogenic Diet in the Treatment of Epilepsy" Medical Clinics of North America 8:1351 (Jan. 1925)

50. Peterman, M.G.; "The Ketogenic Diet in the Treatment of Epilepsy" Wisconsin Medical Journal 25:427 (Sept. 1926)

51. Shaffer, P.S.; "Antiketogenesis" Journal of Biological Chemistry 47:433;449 and 49:143 (1921). 54:399 (1922)

52. Shaffer, P.S.; "Antiketogenesis, Its Mechanism and Significance" Medicine 2:375 (1923)

53. Shaw, E.B.; and Moriarty, M.; "Hypoglycemia and Acidosis in Fasting Children with Idiopathic Epilepsy". American Journal of Diseases of Children 28:553 (1924)

54. Sherman, H.C.; "The Chemistry of Food and Nutrition" MacMillan Co., New York

55. Talbot, F.B.; Hendry, M., Moriarty, M.: "Basal Metabolism of Children with Idiopathic Epilepsy" American Journal of Diseases of Children 28:419 (1924)

56. Talbot, F.B., Metcalf, K.M., and Moriarty, M.; "Clinical Study of Epileptic Children Treated by the Ketogenic Diet" Boston Medical amd Surgical Journal 196:89 (1927a)

BIBLIOGRAPHY

57. Talbot, F.B., Metcalf, K.M., and Moriarty, M.; "Epilepsy: Chemical Investigation of Rational Treatment by Production of Ketosis" American Journal of Diseases of Children 33:218 (1927b)

58. Talbot, F.B.; "The Ketogenic Diet in Epilepsy" Bulletin New York Academy of Medicine 4:401 (1928)

59. Talbot, F.B.; "The Treatment of Epilepsy" The MacMillan Company, New York (1930)

60. Wilder, R.M., and Winter; "The Threshold of Ketogenesis" Journal of Biological Chemistry 52:393 (1922)

61. Wilder, R.M., and Pollack, H.; "Ketosis and the Ketogenic Diet: Their Application to Treatment of Epilepsy and Infections of the Urinary Tract" International Clinics March 1935 Vol.I, page 1

62. Wilkins, L.; "Progress in Pediatrics - Present Status of Epilepsy" International Clinics (1933) 2:265

63. Wilson, G. and Limberger, W.A.; "Dehydration" Journal A.M.A. 101:110 (1933)

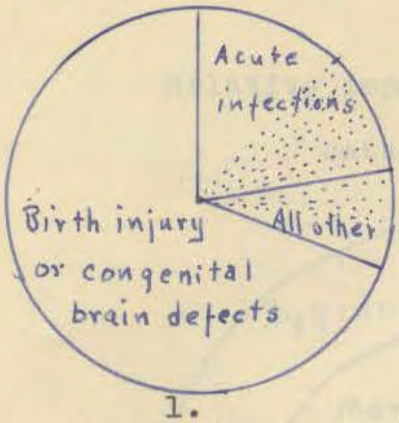
64. Woodyatt, R.I.; "Objects and Methods of Diet Administration in Diabetes" Archives of Internal Medicine 28:125 (1921)

65. Wortis, B.; "Experimental Convulsive Seizures" Journal of Nervous and Mental Diseases 77:233 (1933)

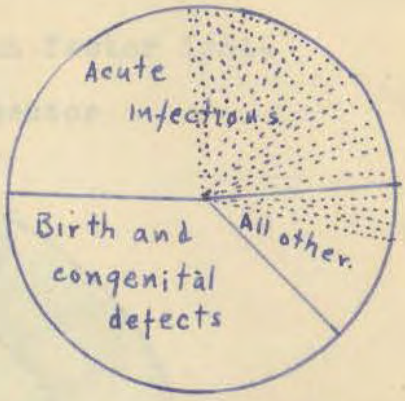
CHART I

CAUSES OF CONVULSIONS AT DIFFERENT AGE PERIODS

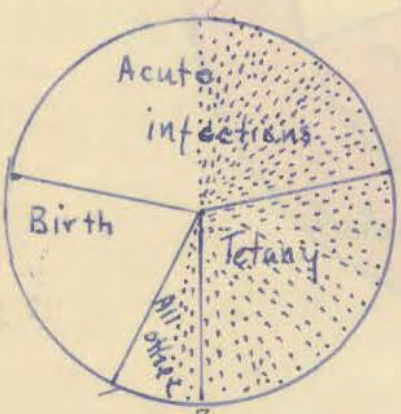
Stippled areas - functional
Unstippled areas - organic



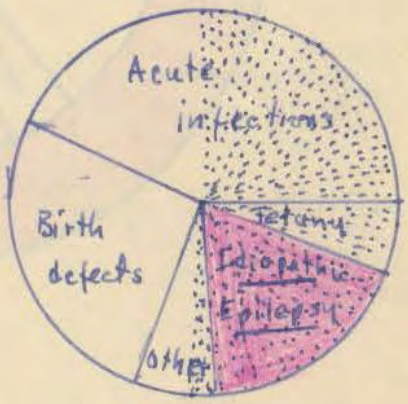
1.
Up to 1 month



2.
1 Month to 4 months



3.
4 Months to 2 Year



4.
2 years to 6 years

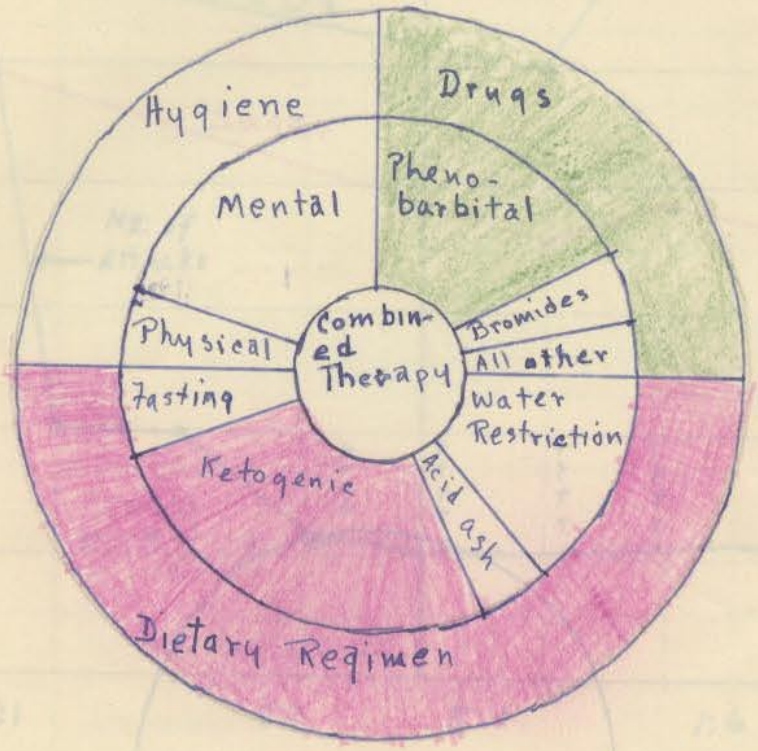
5.
Beyond 6 years

from McQuarrie
Calif. & Western
Medicine 41:10
(1934)

FIGURE I

GRAPHIC REPRESENTATION OF THE VARIOUS ASPECTS OF ANTI-EPILEPTIC THERAPY AS APPLIED TO CHILDREN

Relative importance of each factor indicated by size of sector

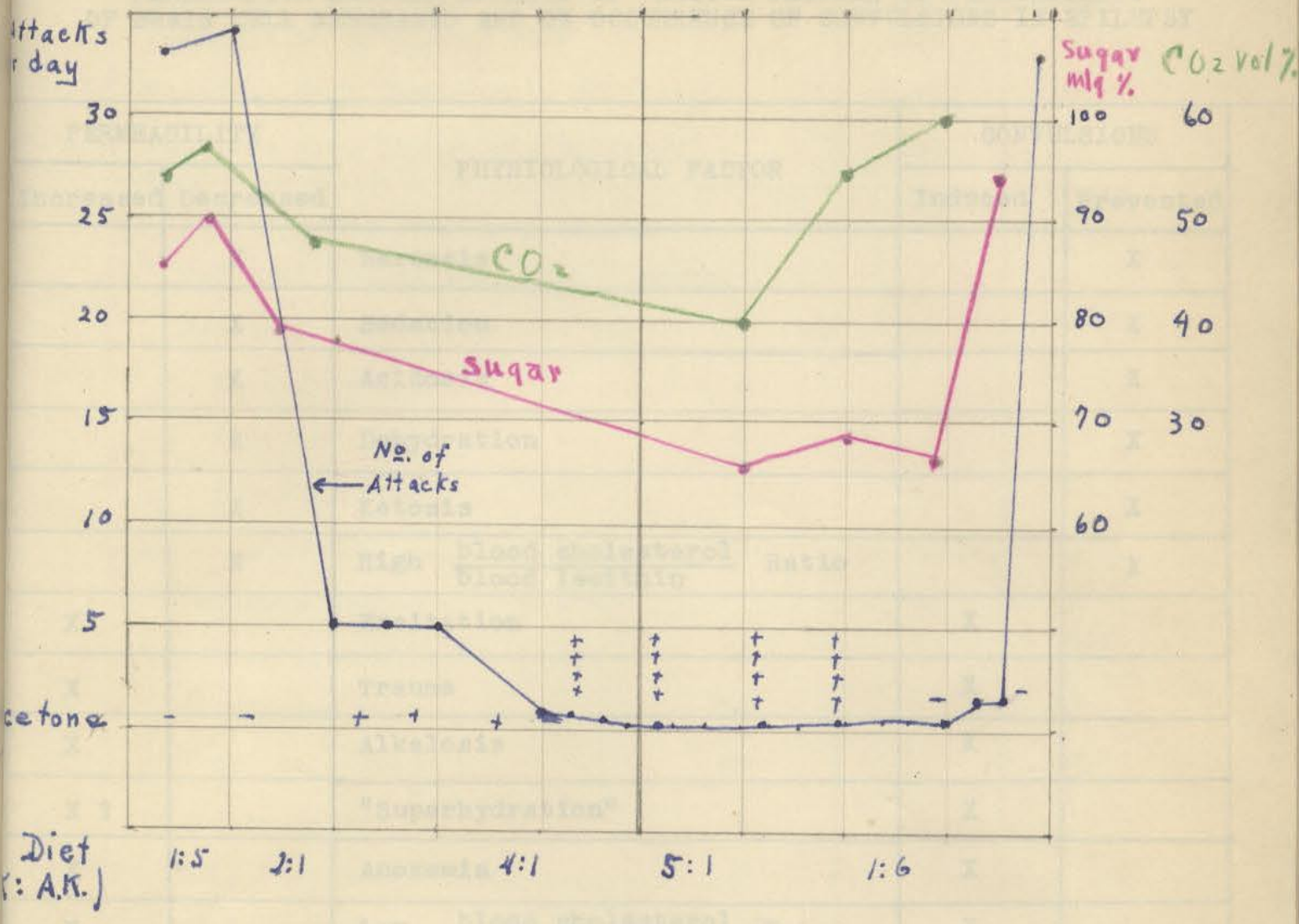


from McQuarrie,
California and Western
Medicine 41:10 (1934)

FIGURE II

RELATION OF ATTACKS TO CHANGES IN THE BLOOD

CHEMISTRY DURING KETOGENIC DIETING



from: Boston Medical and Surgical
Journal 196:89 (1927) T.M.M.

TABLE I

PARALLELISM BETWEEN EFFECTS OF VARIOUS FACTORS ON PERMEABILITY OF BRAIN CELL MEMBRANES AND ON OCCURRENCE OF CONVULSIONS IN EPILEPSY

PERMEABILITY		PHYSIOLOGICAL FACTOR	CONVULSIONS	
Increased	Decreased		Induced	Prevented
	X	Narcosis		X
	X	Sedation		X
	X	Acidosis		X
	X	Dehydration		X
	X	Ketosis		X
	X	High $\frac{\text{blood cholesterol}}{\text{blood lecithin}}$ Ratio		X
X		Excitation	X	
X		Trauma	X	
X		Alkalosis	X	
X ?		"Superhydration"	X	
X		Anoxemia	X	
X		Low $\frac{\text{blood cholesterol}}{\text{blood lecithin}}$ Ratio	X	
X		Hypocalcemia	X	
X ?		Hypoglycemia	X	

FROM McQuarrie,
Calif. and Western Medicine
41:1 (1934)

TABLE II - SUMMARY OF RESULTS

		Patients	%
Patients on Ketogenic Diet		369	
Patients with Symptomatic Epilepsy		51	
Patients with Idiopathic Epilepsy		318	
Patients who failed to cooperate	89		
Patients healed less than 6 months	22		
Patients treated for one year	20		
Free from attacks	4		
Improved	9		
Not benefited	7		
Patients healed 1 year		160	
Free from attacks	58		36
Improved	34		21
Not benefited	68		43
Unclassified	4		
Well, not due to diet	9		
No information	14		

from: Collected Papers of Mayo Clinic 25:1082 (1932)
(Helmholz and Keith)

TABLE III

Status 1927	Case	Status in 1932			
		Cured	Improved	No Benefit	No coop.
Free for more than 1 yr	18	12	5		1
Free for 1 yr. or less	8	6	2(1930)		
Attacks on resuming normal diet	3	1	1		1
Improved	20	1	3	7	9
1930					
Free more than 1 year	42	35	5		2
Free less than 1 year	11	7	3		1
Improved	41	6	15	3	16

from: CollectedPapers of Mayo Clinic 25:1082 (1932)
(Helmholz and Keith)

TABLE IV

	Cases	Ketosis always present	Ketosis Periodic	Ketosis always absent.
Controlled	12	11	1	- -
Improved	44	22	14	8
No benefit	44	13	8	23

TABLE VI

Children	Number of Patients	Percentage of: Complete Relief	Improvement	Failure
Peterman (1926)	70	54	32	
Helmholz	91	31	23	32
Luther	27	33	41	26
Talbot	20	25	45	30
Adults		Number	Number	Number
Barborka	32	7	12	13

TABLE VIII

COMPARATIVE RESULTS OF CALCULATING THE K:A.K. RATIO OF THE DIET BY THE METCALF AND MORIARTY, THE WOODYATT, AND THE SHAFFER FORMULAE

DIET COMPOSITION	M.& M. (grams) F/P/ C	Woodyatt (grams) F.A/G	Shaffer Mols K:A.K.
C=66 P=40 F=159	1.5:1	1.53:1	1.02:1
C=44 P=40 F=168	2:1	2.1 :1	1.4:1
C=20 P=40 F=180	3:1	2.96:1	1.97:1
C= 6 P=40 F=184	4:1	3.9 :1	2.6 :1

TABLE IX

EFFECT OF HIGH-FAT LOW-CARBOHYDRATE DIET ON RETENTION OF PROTEIN

K/A.K.	Grams of F. C. P.	Urinary Protein Grams N_2 x 6.25	Protein Balance (Stool N_2 not included) Grams	Length of Period	
1:6	56 296 40	22.1	/ 17.9	5 days	No Ketosis
		18.3	/ 21.7	5 days	
		24.3	/ 15.7	5 days	
1:2	109 177 40	28.1	/ 11.9	5 days	No Ketosis
		26.1	/ 13.9	5 days	
		26.1.	/ 13.9	5 days	
3:1	180 20 40	30.6	/ 9.4	5 days	Ketosis
4:1	185 6 40	37.0	/ 3.0	5 days	Marked K.
		28.5	/ 11.5	5 days	
		37.0	/ 3.0	5 days	

TABLE X

ESTIMATED TOTAL CALORIC REQUIREMENTS FOR CHILDREN OF DIFFERENT AGES

Age in Years	Minimal Basal + 50%		Maximum	
	Boys Calories	Girls Calories	Boys Calories	Girls Calories
1	900	900	900	900
2	975	960	1200	1200
3	1050	1040	1300	1300
4	1100	1050	1400	1400
5	1200	1125	1500	1500
6	1275	1200	1700	1600
7	1350	1275	2000	1800
8	1425	1325	2500	2000
9	1500	1375	2600	2300
10	1575	1425	2800	2400
11	1650	1500	3000	2600
12	1725	1560	3250	2900
13	1800	1610	3500	3200
14	1975	1650	3750	3400
15	2050	1680	4000	3600

TABLE XV

GENERAL GUIDE FOR CALCULATING DIET

No.1 For children for Pre-school age (body weight up to 19 kg.)

Total water - - - 40-30 gm. per kgm. body weight
Protein - - - - 2.0 gm. per kgm. body weight
Carbohydrate - - - 0.7 gm. per kgm. body weight
Fat (gm) = $\frac{60 \times \text{Kg. of body weight}}{9}$

No.2 For children for 5-10 years of age (20-32 Kgm. weight)

Water- - 30-20 gm. / Kg.
Protein - 1.5 gm. / Kg.
Carbohydrate - 0.5 gm. / Kg.
Fat (gm) - - - $\frac{50 \times \text{Kgm. body weight}}{9}$

No.3 For children 10 years plus (33 Kgm. plus weight)

Water - - - 25-15 gm. / Kg.
Protein - - 1.5 gm. / Kg.
Carbohydrate - 0.4 gm. / Kgm.
Fat (gm) - - $\frac{40 \times \text{Kgm body weight}}{9}$