THE KETOGENIC DIET IN EPILEPSY.

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In recent years new avenues of approach to the treatment of epilepsy have been opened up, investigation and experiment have been stimulated, and, especially in young patients, definite hopes of cure have been held out. Experiments in metabolism have shown that a condition of acidosis is antagonistic to epileptic seizures. The ketogenic diet is one designed to produce acidosis artificially, this being achieved by reducing the carbohydrates and greatly increasing the fats.

For hundreds of years it had been known that fasting has a beneficial influence on epileptics, reducing the number of convulsions and ameliorating the mental depression and anguish. This effect of fasting was attributed to many factors, but careful inquiry was not made until recent years. In 1921 Wilder (1) maintained that the ketosis invariably associated with fasting was the factor responsible for the good results in epilepsy. However, since many diseases are favourably influenced by fasting, much more was needed than a mere statement to prove that the ketosis was responsible. This led to patients being treated therapeutically in order to produce an artificial ketosis, a ketosis not dependent on the amount of food consumed. Consequently workers in the Mayo Clinic started a system of dieting in epileptic adults that had the production of ketosis as its object. The results were indifferent, but in 1922 Helmholtz (2) treated children in this manner, and found that 31% were free from attacks and 23% benefited. The remaining 46% were not improved. Later, in 1924, the Mayo Clinic again started the treatment of selected cases in adults, with more encouraging results than the first trial.

No abnormal ingredient is consistently present in the urine of epileptics, neither are any of the normal constituents greatly increased or reduced, with the possible exception of ammonia. According to Bisgaard and others the ammonia is increased in the urine in epileptics, but bears no direct relation to seizures. They have worked this out on the basis of Hasselbalch's formula, namely, that in healthy subjects the ratio of ammonia nitrogen to the total nitrogen of the urine, if plotted against the pH of the urine, gives a fairly constant value. This work has focused attention on acid-base equilibrium. Many workers have given data on pH values in the blood of epileptics, and it is

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now generally accepted that although there is no persistent and consistent abnormal equilibrium, there is an unusual degree of fluctuation in pH values between normal limits from day to day, with a tendency to a more alkaline reaction.

The rationale of the ketogenic diet is based on the foregoing observations. It is an attempt to upset the acid-base relations in the patient by giving a bias towards acidity. Apart from independent observations on the subject conducted in a pure spirit of inquiry, there is much empirical evidence in support of the view that acidosis is antagonistic to the convulsive habit. As stated above, fasting has a favourable influence on the epileptic, and has been practised therapeutically for hundreds of years. Chemically the essential changes produced are in the direction of acidosis. Breathing of CO_2 also inhibits convulsions—a condition again tending to acidosis.

Very few observations on this subject of ketosis have been carried out in this country, so that an investigation into the claims made abroad is overdue. It will also be considered how far such a diet is practicable. It must be borne in mind that a treatment depending on self-sacrifice and great self-control is not easy of accomplishment, so that it would appear as if institutional patients who are continually under observation should be the best subjects for experiment.

The present investigation is on 20 cases of idiopathic epilepsy—that is, epilepsy in which there is no apparent organic lesion. The patients have not been selected because of preconceived ideas of their likelihood to react well, but with the view of testing the diet in all types of major epilepsy. Care has been taken to have representative cases. Thus some have many fits, others have few; some are bright and cheery, others are dull and demented. Many of the cases have violent bouts of excitement.

The average number of fits per month of the patients chosen for the diet ranges from 3·4 to 29·2. All these patients have major epileptic fits. As regards mental condition, 8 of the patients can give a good account of themselves, and are well behaved, except before and after fits. Five of these 8 employ themselves usefully. Six patients are of the demented class, who can give little account of themselves, and who are idle and apathetic except at "fitting" periods. The remainder (6 patients) are in a class between these two extremes, patients who, although able to give a fair account of themselves, are idle and apathetic, and at times violent and troublesome. The patients were equally distributed among three wards, so that the nursing problems could be reduced as far as possible.

To produce ketosis in a normal individual the conditions present in diabetes must be reproduced. This is done by limiting the carbohydrate to a very low point and increasing the fat to a very high point. The diet must finally show that fat is contributing at least four times the calories derived from carbohydrate and protein combined. For an effective ketosis, at least in

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adults, it may be necessary to raise the fat quota so that eight times as many calories are being derived from fat as from carbohydrate and protein. The degree of ketosis can be roughly measured by the intensity of the reaction given by the urine to the nitroprusside test.

The method of calculating the diet required for each patient was according to the tables set out by Barborka (3), who worked on the subject in the Mayo Clinic. The data were taken from the works of Du Bois, and of Boothby and Sandiford.

The first requirement was a diet so calculated that the patient was receiving sufficient food to provide the calories for his energy requirements and the maintenance of weight. These calories were given to the patient in the form of carbohydrate, protein and fat. At first, however, it was necessary to test the diet in order to discover whether the caloric requirements were correct so for ten days a non-ketogenic diet was calculated for each patient. According to Woodyatt and Wilder, the amount of carbohydrate in grammes in a progressively ketogenic diet is found by multiplying the total calories needed by factors ranging from 0·035 to 0·006. In the first diet, therefore, the carbohydrate ratio was calculated by using the greater factor. The protein requirements in grammes is estimated as one-third of the body-weight in pounds. The fat quota is obtained by multiplying the total calories required by 0·09 or 0·10.

Since the amount of carbohydrate in the diet is very small, it is considered wise to reach a true ketogenic diet in easy stages. Therefore at least two diets are interposed between Diet I and the diet necessary to produce ketosis without fail. The carbohydrate being withdrawn gradually, the patient is more willing to co-operate. In the second diet (after any necessary alterations have been made in the total caloric requirements as shown by Diet I), the carbohydrate allowed is four-sevenths of that in Diet I. In Diet III this amount is reduced to three-sevenths, and in Diet IV (the ketogenic diet used in the present series of cases) to less than two-sevenths. To allow for the calories lost by the reduction in carbohydrate the fat is increased slightly.

For convenience, those patients who weighed within a few pounds of each other were treated as if they were the same weight.

In calculating the quantities of the various foods the tables of Harrison and Lawrence (4) were used. These tables are compiled from the work of many authors, and give a good working standard.

There are great difficulties in devising these diets. The patients have all been used to high carbohydrate meals, so that ketogenic diets are apt to be nauseating. Carbohydrate articles of diet are much more bulky than protein and fat articles, so that a meal looks very small and insufficient. At the same time small concentrated meals rarely relieve the feeling of hunger that the patient brings to the table. As far as possible, therefore, vegetables containing small amounts of carbohydrate were used instead of potatoes. Another, and

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perhaps greater, hardship, is the cutting down of bread. Bread is the staple article of diet of all the patients in this hospital, so that at meal-times the ketogenic patients cast envious glances at the liberal helpings of their more fortunate friends. It was necessary, of course, to give the selected patients their meals at separate tables, specially looked after by a nurse.

It was explained to all the patients capable of appreciating the points exactly what was intended and what was expected. It has always been our experience that epileptics are easy to handle when they believe that something special is being attempted on their behalf. They will put up with many hardships, and at times, gladly accept the rôle of martyr. The other patients in the ward were warned that no food or sweets of any kind were to be given to the special patients. To guard against surreptitious eating was particularly difficult, since some of the chosen epileptics had as close friends patients who were liberally supplied with fruit, sweets and extra food. However, frequent examination of the urine for acetone bodies was a good check, and timely warnings to suspected patients often had the desired effect. If the urine showed no acetone bodies, the patient was immediately taxed with eating extra food, and it was remarkable how often a confession of guilt was received, followed by a resolution to do better in the future. On the whole the regime was well maintained—better than could have been expected. A great deal of the credit is due to the nursing staff, who entered into the task with enthusiasm—an enthusiasm quickly communicated to the patients concerned.

A typical day's diet for one of the patients was calculated as follows: The total caloric requirements of patient M. G— were 1,712 calories. Of this total 10·2 grm. of carbohydrate were to supply 42 calories; 35·6 grm. of protein were to supply 140 calories; and the remainder was to be supplied by fat. It was considered a better idea to assign the protein and fat elements before making up the carbohydrate quota, because the type of carbohydrate food required depends to some extent on the fat and protein content of the meal. Protein was made up mainly from meat, bacon, cheese and eggs; fat from butter, cream, bacon, cheese and cod-liver oil. The carbohydrate was made up mainly from bread, and from those vegetables having a poor carbohydrate content.

TABLE I.

	Ozs.	C.	P.	F.	Total calories.
Bread	½	7·5	3	..	43
Vegetables	3	2·5	..	..	10
Meat	2½	..	16	16	214
Bacon	2	..	10	30	311
Butter	2	..	..	50	465
Cheese	1	..	7·5	7·5	100
Cream	2	..	..	20	186
Cod-liver oil	1½	..	..	45	418

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This diet was made up into meals in the following manner. Breakfast consisted of bacon 2 oz., bread ¼ oz., butter 1 oz., cream 1 oz. Tea (unsweetened) was given *ad lib.* For dinner the patient had meat 2¼ oz., and vegetables 3 oz. For tea the menu was bread ¼ oz., butter 1 oz., cream 1 oz., cheese 1 oz. Again unsweetened tea was given *ad lib.* After each meal ½ oz. of cod-liver oil was given. For variety the vegetables could be changed frequently, a choice of the following being allowed: Sprouts, cabbage, tomato, cauliflower, swede and lettuce. Instead of cheese, one egg was allowed for every ounce. If the diet was calculated to contain 2 oz. of cheese, then it was found advisable, despite the extra cost, to give an egg in lieu of 1 oz. of cheese. Some patients objected at first to cod-liver oil, but they were few, and they soon came to look upon it as a medicine for their own good. At times cream or butter was substituted for part of the oil. However, if that were done, the patient found it difficult to consume so much butter and cream without the help of bread or fruit.

On the whole the diet was well tolerated and the complaints were dealt with easily. The greatest difficulty was the small amount of bread. A diligent search was made for a very low carbohydrate bread, such as is used in severe diabetes, but no firm was able to furnish a sample that was satisfactory. The lower the carbohydrate content, the dearer was the bread, and even the samples containing least carbohydrate would not have been bulky enough for our purpose. Everything considered, it was decided to continue with ordinary bread. Various kinds of bran wafers were secured, but the patients did not take kindly to them, and they were discontinued.

Constipation, generally complained of by epileptics, was treated by weekly doses of magnesium sulphate, but no great difficulties were encountered in this respect, as the ketogenic diet is fairly laxative.

The urine of every patient on the diet was examined twice weekly for acetone bodies. If the patient was faulty in habits, catheter specimens were obtained.

If the urine of any patient was found to be negative a special watch was kept on that patient, and if it remained negative the carbohydrate quota was cut down.

Before treatment commenced a special mental and physical examination was made of each patient, so that a comparison could be effected, apart altogether from the number of fits.

Results of Treatment.

It is now intended to present the salient features of the treatment and its results in a series of tables, which will show at a glance the various points brought out. First of all is a record of the fits each patient had in each month, covering the whole period under review—that is, 16 months.

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TABLE II.

	Number of fits during eight months before treatment began.								Total.	Number of fits during the eight months of treatment.								Total.
	1st.	2nd.	3rd.	4th.	5th.	6th.	7th.	8th.		1st.	2nd.	3rd.	4th.	5th.	6th.	7th.	8th.	
A. A—	34	11	32	45	20	21	35	36	234	24	42	43	14	35	44	34	28	264
E. R—	33	32	28	28	26	27	29	11	214	36	28	25	26	25	20	8	13	181
M. T—	11	9	24	4	24	40	30	19	161	7	3	10	10	12	18	9	13	82
R. P—	19	26	13	21	21	20	21	18	159	19	9	13	21	22	6	8	18	116
M. W—	2	3	4	5	9	10	107	9	149	9	8	10	9	29	4	15	20	104
N. K—	8	3	11	17	16	11	13	7	86	14	11	11	10	33	Died.			79
M. G—	6	4	12	10	10	22	9	7	80	2	2	2	2	0	2	1	2	13
H. P—	17	3	11	5	6	10	7	6	65	14	8	8	4	7	4	1	5	51
B. C—		(Before admission)				6	14	3	23	1	5	5	7	6	3	4	1	32
F. L—	7	8	8	5	9	10	10	4	61	6	7	10	6	8	15	1	8	61
A. F—	9	9	3	6	4	14	7	5	57	5	9	4	7	5	8	4	9	51
A. H—	4	7	7	8	13	6	2	5	52	1	3	5	6	3	1	3	3	25
R. R—	10	1	8	8	7	7	2	3	46	7	9	10	2	7	8	8	14	65
E. W—	3	4	8	7	6	7	7	2	44	6	7	7	8	9	6	6	6	55
A. Gr—	11	4	8	4	4	3	5	1	40	0	0	0	0	Died.				0
M. A. B—	3	3	2	3	7	9	9	8	44	0	10	1	3	3	7	5	1	30
A. Ga—	4	4	9	2	3	4	7	3	36	6	6	4	3	22	7	6	4	58
M. E. C—	2	4	7	6	2	4	3	4	32	3	2	3	1	4	2	2	0	17
E. T—	4	4	3	2	3	6	4	5	31	5	3	4	6	3	4	5	1	31
A. C—	4	4	3	7	6	2	0	1	27	0	2	0	0	0	1	2	2	7

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It will be noted that of the 20 patients, 13 had a reduction in fits, 2 were quite unchanged, and 5 had an increase. Thus, as regards actual fits, 65% were relieved, 10% were unchanged, and 25% reacted badly. In an institution where large numbers of epileptics are living together, any substantial reduction in the number of fits is a boon both to patients and staff, so that the above figures are considered satisfactory.

In the individual reports of each patient the fits were divided into day and night fits. Some patients habitually have more day fits than night fits, and *vice versa*. It is interesting to note what effect the ketogenic diet has on the time incidence of fits. Only five patients had an absolute increase in fits, yet 9 patients had an increase in night fits, and only 4 had an increase in day fits. Of those having an increase during the day, 2 also had an increase during the night. All the patients having an absolute increase of fits had an increase during the night. Three patients had increased night fits, though over the whole period they showed a decrease in fits. This would seem to show that it is during the night, in the period when the patient is furthest from his meal, that any increase in fits generally takes place (during ketosis). This is also the period when ketosis is at its lowest. It is always better for an epileptic to have his fits at night, since he cannot injure himself, and since it does not interfere with his daily task. Most epileptics would gladly welcome a regime that changed their time of fits from day to night. Therefore this result of the treatment can also be considered satisfactory.

The next table shows the fluctuations in weight over the same period of time. The weights were taken weekly and tabulated so that a strict watch could be kept. The diet in several patients was frequently adjusted at times to maintain ketosis, at other times to maintain weight.

TABLE III.—*Weight in lb.*

	July.	Aug.	Sept.	Oct.	Nov.	Dec.	Jan.	Feb.	Mar.
A. A—	94	94	89	92	92	91	92	92	95
E. R—	104	104	102	102	101	100	98	99	99
M. T—	155	160	151	148	149	146	145	142	140
R. P—	118	119	118	119	121	121	120	115	115
M. W—	91	91	90	91	96	98	98	Discontinued.	
N. K—	90	87	85	86	86	87	Deceased.		
M. G—	107	107	107	109	109	108	109	104	98
H. P—	114	112	113	114	116	118	118	118	119
B. C—	112	110	119	114	112	112	111	112	108
F. I.—	112	112	112	111	114	115	119	116	118
A. F—	148	142	144	145	149	150	148	148	152
A. H—	105	105	108	109	104	103	108	106	105
R. R—	124	124	123	122	120	119	120	118	116
E. W—	104	106	103	103	108	105	108	103	107
A. Gr—	101	100	98	99	97	94	Deceased.		
M. A. B—	120	116	110	108	108	107	107	108	108
A. Ga—	132	133	132	131	131	132	131	128	132
M. E. C—	122	119	118	118	114	116	114	112	114
E. T—	122	116	117	117	114	115	115	115	117
A. C—	118	112	115	112	111	111	108	108	110

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Comments.

As was to be expected, most of the patients lost weight, but on the whole the losses were within reasonable limits, and not one patient appeared the worse for it. It is significant that, of the 5 patients who did not benefit from the treatment, 3 increased in weight, and of the other 3 who gained in weight, only 1, H. P—, was really considered to have benefited from the diet. Thus it would seem as if a diet low in caloric value is of advantage to epileptics.

The epileptics in this hospital are all certified patients, so that the mental attitude and the behaviour are as important as the number of convulsions.

The following table shows the mental reaction to the ketogenic diet. Any improvement is a distinct gain to an overworked and harassed staff.

Mental Reaction.

A. A—	Not improved.	A. F—	Not improved.
E. R—	Improved.	A. H—	Improved.
M. T—	Not improved.	R. R—	,,
R. P—	Improved.	E. W—	Not improved.
M. W—	Not improved.	A. Ga—	,,
N. K—	,,	A. Gr—	,,
M. G—	Improved.	M. A. B—	,,
H. P—	,,	M. E. C—	,,
B. C—	Not improved.	E. T—	,,
F. L—	,,	A. C—	Improved.

It will be noted that seven of the patients improved mentally. This was reflected in fewer attacks of excitement and violence, less tendency to quarrel, and the making of fewer false accusations. Indeed it was observable on this last head that some patients who habitually complained of ill-treatment and lack of consideration began to praise the staff and show appreciation of any little kindnesses. As has been noted before, this type of improvement may be due to more time being devoted to the patient. Only one patient improved mentally who showed an increase in the number of fits (patient R. R—. This patient also improved physically). All the other patients who improved mentally also had fewer convulsions. On the other hand 7 patients had fewer convulsions, but did not improve mentally. However, when it is considered that all the patients were institutional chronics, in whom intellectual deficiency was the rule, it will be seen that improvement could only be expected in the more troublesome and violent.

When the influence of weight is taken into consideration, only one patient improved mentally who gained in weight. This is contrary to what one would expect, since most patients who gain weight become less troublesome and more easily managed. A gain in weight is often the first objective of treatment in insanity, so that the above result is strange. However, when it is also noted that only two patients who gained weight had fewer fits, it suggests that a much lower diet in calorie value might be given to all epileptics with advantage.

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Apparently over-feeding does not agree with them. Another explanation is that most of the patients who gained weight might have had access to more food, but with the exception of one patient (E. T—), the ketosis was maintained well throughout the whole period, as shown by the acetone content of the urine. The patient mentioned was young, was given many privileges, and was much above the average in mental acumen ; but she lacked a sense of responsibility, and she stooped to many dodges to get more food, especially fruit and sweets.

Put shortly, then, the complete results of the ketogenic diet in the 20 cases under consideration are as follows: 60% had a reduction in seizures (one patient was completely free from seizures); 10% were quite unchanged; 30% had an increase in seizures, 35% improved mentally, and 65% were unchanged mentally.

The results of other investigations show that the above are a fair average. Most experimental diets have been on children. Peterman (5) treated children with a diet in which the ratio of calories from fat are 2, 3 or 4 times the total calories from protein and carbohydrate. His results were that 57% were free from fits, 25% were improved, while the remaining 18% were not improved. He found that the younger the children, the better the results, and that *petit mal* attacks were more easily controlled than the major attacks.

Luther and Moriarty (6) had a series of 27 patients: 33% were free from seizures, 41% were improved, and 26% were unchanged. All the patients who were freed from seizures were under 13 years of age.

The results of Helmholtz (2) in the Mayo Clinic are as follows: 31% were free from attacks, 23% were improved, 46% were unchanged. These patients were all children, and the results agree fairly well with those of Luther and Moriarty.

Weeks, Allen, Rennen and Wishart (7) fed 6 adult institutional epileptics with a very high fat diet (up to 580 grm. of fat and only 4 of carbohydrate). They concluded that there was no effect on the number of seizures. Barborka, however, beginning in 1924, treated 49 epileptic adults by the ketogenic diet. His results were: 14·3% free of seizures, 25% improved, 26·5% were not improved, while the remaining 34·2% were only on the diet from 2–4 weeks. His results therefore showed that nearly 40% were definitely improved.

Bastible (8) reported a series of 29 cases of epilepsy, mostly of the *grand mal* type in adult females, treated by ketogenic diet. He included biscuits made from bran and Carrigeen moss. He found a reduction in fits in 20 cases, and cessation in 2. Later he combined the treatment with the exhibition of acid salts and concluded that this had a beneficial effect. He was of the opinion that the ketogenic diet was worth an extended trial.

Conclusions.

The foregoing results show that even in institutional epileptics of the lowest grade, ketosis engendered by a high fat diet is antagonistic to seizures in a fair

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number of patients. The results do not compare very favourably with those gained by Helmholtz in children, but it has always been recognized that adults are particularly resistive to treatment. Neither are the results good compared with Barborka's as regards complete cessation of fits. He treated 32 adult patients, but it must be remembered that Barborka's patients were not of the institutional class, but selected cases in which the epileptic attacks were the only evidence of abnormality. At the same time the Mayo Clinic patients were suffering mainly from *petit mal*, whereas this investigation has been carried out in patients who were having *grand mal* attacks.

The results show that in adult epileptics of the chronic class, much can be done to reduce seizures and limit impulsive behaviour by the use of the ketogenic diet. That 65% of patients are greatly relieved is assuredly a good result, especially when dealing with a seemingly hopeless type of case. There are difficulties in maintaining the diet, but in well-regulated hospitals it is by no means above the talents of the staff.

The reason why ketosis should limit the number of convulsions in epilepsy is not easy to discover, but the following observations do throw some light on the problem.

If the establishment of acidosis in epilepsy is of value in treatment, then it follows that the administration of alkali should result in an increase in seizures. In the cases in which this has been done the results are striking. As far back as 1897 Charon and Briche (9) (who believed that acidosis was present in untreated epileptics) gave subcutaneous injections to 8 patients who showed an increased frequency in the fits. Lennox and Cobb (10) gave alkali to a fasting epileptic with a resulting increase in seizures. Another patient of theirs, in whom acidosis had been induced, first by fasting, and then by administration of $CaCl_2$, was given alkali after each period of acidosis. The result was a great increase in convulsions. In some patients, although acidosis is actually present, continued administration of alkali results in seizures. This suggests that it is the sudden change from acidosis to alkalinity that precipitates the seizures.

It has been already stated that hyperpnœa in epileptics frequently results in the precipitation of a seizure. In rapid deep expiratory breathing the patient gets rid of CO_2 from the blood, with the result that the alkalinity increases; a seizure is the result. If, however, the patient is made to re-breathe the air he has actually expired (air now having increasing amounts of CO_2), the expected seizure does not occur. This is apparently due to the high content of CO_2 in the inspired air. Again, if the patient is made to breathe air that has decreasing amounts of oxygen in it without a corresponding increase in the CO_2, seizures result. This last experiment is carried out by making the patient re-breathe the expired air from which the CO_2 is removed. Relating these experiments, and remembering that it is not possible to induce seizures in an epileptic by hyperpnœa if pure oxygen is breathed, it would appear that

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oxygen lack in the tissues is the fundamental condition. Oxygen is given up to the cells much more readily when the percentage of CO_2 in the blood is relatively high, while the converse is equally true. Thus, decreasing the CO_2 of the blood has a similar effect to limiting the oxygen supply. A decrease in CO_2 in blood results in a bias towards alkalinity, therefore acidosis is a condition in which the tissues much more readily receive oxygen, and alkalosis a condition in which the tissues find difficulty in consuming oxygen. Apparently it does not matter a great deal how the acidosis or the alkalinity is produced. In epilepsy the cells most affected are the neurones, and it is well known that in oxygen deficiency the neurone system is the first to suffer. In the normal individual consciousness is lost without actual tonic or clonic muscular spasms, but in epilepsy it is not to be supposed that the nervous system is ordinarily robust. Probably it reacts to much smaller deficiencies in oxygen supply and in an exaggerated fashion.

It is not being suggested that epilepsy is a syndrome depending on an abnormal alkaline bias in the blood and tissues. This may be the cause, but oxygen supply to the tissues can be affected in many ways besides decreasing CO_2 in the blood. For example, the blood supply may be at fault, as in spasm of arterioles, or stasis of the venous return. The arterial spasm theory has many upholders at the present time, but it must be remembered that arterial spasm merely leads to the tissues being starved (principally of oxygen, since the cells react most quickly to it, probably because no tissue interchange can take place without some oxidation process).

The essential cause of epilepsy remains unknown. It is perhaps nearly related to angina pectoris, migraine, and general muscle cramps. All these conditions are alike in that there may be many precipitating factors quite different from the essential cause.

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