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Review

History of dietary treatment from Wilder's hypothesis to the first open studies in the 1920s

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ABSTRACT

In the ketogenic diet (KD) history, Wilder is often mentioned as the first author to report on the use of KD for patients with epilepsy.
Our article aimed to understand how Wilder formulated the hypothesis of the KD effectiveness for patients with epilepsy, and how the KD was used and spread in the 1920s.
In 1921, Wilder published two articles on the effects of ketonemia on epilepsy. He first reported on the interest of fasting for patients with epilepsy, suggesting that the benefits of fasting on seizures might be dependent on ketonemia. He then hypothesized that equally good results could be obtained with a KD, very rich in fat and very low in carbohydrate, which would provoke ketogenesis, and observed the effects of this diet on three patients for the first time.
Following the publication of Wilder articles, 9 papers on KD were published during the 1920s, involving more than 400 patients with epilepsy.
Ketogenic diet therapies (KDT) are now evidence-based treatments of epilepsy. Available experimental data do not confirm the role of ketosis as the unique mechanism of the KD. The KD is still explored to understand all the underlying mechanisms.

1. Introduction

Nowadays, ketogenic diet therapies (KDT) are evidence-based treatments of epilepsy. Several controlled randomized trials have demonstrated the effectiveness of such low-carbohydrate, high-fat diets [1,2]. Recently, international consensus recommendations on the optimal clinical methodology to conduct KDT have been updated [3]. For certain epilepsy syndromes such as Dravet syndrome, epilepsy with myoclonic–atonic seizures, tuberous sclerosis complex, infantile spasm syndrome (West syndrome), and also for Angelman syndrome, mitochondrial disorders, febrile infection-related epilepsy syndrome (FIRES), and refractory status epilepticus, KDT have been consistently reported as particularly beneficial [3].

Initially, the ketogenic diet (KD) was introduced to mimic the effects of fasting on patients with epilepsy, as it could be maintained over time. It is often mentioned that dietary treatments have a long history. One of the earliest reference of fasting and diet therapies as treatment for epilepsy dates approximately from 500 BC. In the Hippocratic collection, a man with seizures was cured by fasting (complete abstinence from food and drink) [4]. Fasting is also reported to treat seizures when Jesus cured a boy with epilepsy by asking him to pray and fast (Matthew 17:14–27) [5,6]. In 1911, Guelpa & Marie published an article on the use of intermittent fasting to treat epilepsy: the diet consisted of daily administration of sodium sulfate for 4 days, with unlimited aqueous beverage and no food, followed by a vegetarian diet restricted to half of the ordinary caloric intake [7]. This was reproduced approximately every 8 days and resulted in the improvement of 6 patients. The history of KDT is often tied to this paper, which is the first report of a dietary treatment for epilepsy [8].

Ten years later, in 1921, Wilder published consecutively two articles on the effects of ketonemia on epilepsy [9,10]. Many scientific papers quote Wilder articles as the first report of the use of KD. In 2004, Wheless published a chapter in a book called *Epilepsy and the Ketogenic Diet* on the history and origin of the KD, quoting the two Wilder papers [6]. In other recent papers written by Nylen et al. [11], Sampaio [12], and Kim [13], only one of the articles published by Wilder is quoted. One century later, we searched for Wilder papers and the available data in the 1920s to observe how the use of KD in patients with epilepsy was initially reported.

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Table 1
Summary of the patients' characteristics, methodology, and results of the papers on ketogenic diet published in the 1920s.

Summary of the patients' description, the methodology, and the results			
Article	Patients	Methodology	Results
Geyelin (1921) Fasting as a method for treating epilepsy, *Medical Record*, 99:1037–1039 United States of America	3 patients with epilepsy treated by Dr. Conklin; then 1 patient treated by Dr. Geyelin before forming a large group of 26 patients.	To confirm if seizures stop in a large group of patients with epilepsy treated with fasting, and to see if there is a particular type of epilepsy that would be more suitable for this type of dietary treatment.	Geyelin observed 3 patients with epilepsy treated by the osteopath Dr. Conklin who applied a fasting period of 15 days, followed by a feeding period of 3 weeks, and then by a second fasting period of 4 to 5 days. There were 4 periods of fasting during several months. In 1 patient, seizures stopped after the 2nd day of fasting. One patient remained seizure-free for 2 years and 1 for 3 years. After that, Dr. Geyelin treated 1 patient with "grand mal" seizures with fasting, and seizures stopped on the 2nd day of the fast. The patient has been seizure-free since; however, the fast had to be stopped on the 3rd day because the patient presented severe acidosis. Then, 26 patients with epilepsy started very short fasts: 1st 3 days, 2nd 5 days, and 3rd 10 days. Patients did not show discomfort. Finally, the length of fast adopted was 20 days. After 10 days of fasting, 4/26 patients presented with epileptic symptoms. Acid excretion rose during fast and decreased to its original level before the fast on the 21st day. Two of 26 patients remained seizure-free for 1 year or over a year, 6/26 treated by 1 or 2 fasts did not show any improvement, and 18/26 cases showed marked improvement. Patients lost weight. Two of 26 developed marked sinus arrhythmia on the 14th day of fast (aged 15 and 18 years old), 1 girl aged 13 years developed bradycardia, and 1 patient developed maniacal symptoms during 36 h, which disappeared without stopping the fast. The majority of cases with high acid excretion showed greatest improvement. All patients regained their body weight within 3 weeks and did not present any side effects following the fast. Dr. Geyelin said that the fasting treatment is "*by no means a cure-all*".
Wilder (1921) The effects of ketonemia on the course of epilepsy, *The Clinic Bulletin*, 2:307. United States of America	"*A fairly large number of patients*" with severe cases of epilepsy. No exact number of patients is given.	Wilder reported on results obtained at the Presbyterian Hospital, New York, by Dr. H. R. Geyelin. Patients were subjected by Dr. Geyelin to periods of absolute fasting.	"*A good proportion of patients*" (no exact number is given here but more precisions are given in Geyelin paper) subjected by Dr. Geyelin to absolute fasting remained seizure-free during the fasting period and for several months after stopping the fasting and returning to normal diets. Wilder hypothesized that the benefits observed by Dr. Geyelin may depend on the ketonemia, which may result from fasting, and that possibly equally good results could be obtained with ketonemia produced in another way. Diets very rich in fat and very low in carbohydrate can provoke ketogenesis. Wilder then proposed to test the effects of these ketogenic diets on a series of patients with "*essential epilepsy who are having attacks of grand mal or psychic equivalents at frequent intervals, two or more a week*". Wilder would like to realize this trial at the hospital in order to quantitatively control the food intake and follow the effects by repeated analysis of blood and urine.
Wilder (1921) High fat diets in epilepsy, *The Clinic Bulletin*, 2:308. United States of America	Three cases with epilepsy treated with the ketogenic diet. **Patient n°1:** A boy aged 13 years with epilepsy–migraine syndrome. Familial history of migraine. Since 6 or 7 years old, the patient had migraines. Seven months	First application of a ketogenic diet on patients with epilepsy.	**Patient n°1** was admitted to the hospital on June 13, 1921 and placed on observation diet. On June 17, he suffered from 2 severe and typical convulsions. The diet was then modified to 15 g of carbohydrate, 57 g of protein, and 231 g of

Table 1 (*continued*)

Summary of the patients' description, the methodology, and the results			
Article	Patients	Methodology	Results
	ago, he had a "*typical epileptic convulsion*" with loss of consciousness and since then 2 or 3 seizures/week. He presented a slight congenital deformity of the spine. **Patient n°2**: A man aged 31 years with essential type epilepsy. Familial history of migraine-like headaches. The patient had convulsions for 3 years, increasing in frequency (3 or 4/week for the last few months). He had mitral stenosis, extrasystoles, and arteriosclerosis. **Patient n°3**: A woman aged 23 years with epilepsy without history of heredity. She had convulsions for 5 years, recently with a frequency of 1/week.		fat, which quickly resulted in ketonemia and acetonuria. The patient was seizure-free for the following 2 weeks. Then, possibly precipitated by an attack of tonsillitis, the patient had 2 convulsions. Since then, the patient was seizure-free for nearly 4 weeks. The patient was satisfied with his diet, was maintaining his weight, and was feeling well subjectively. **Patient n°2** was admitted to the hospital on June 19, 1921 and immediately started a ketogenic diet. On the following day, convulsions occurred, after which he remained seizure-free for 3 weeks. He suffered from a severe convulsion when he went to a circus on July 9 and from 2 very mild attacks of "petit mal" 2 days later. He went home on July 16 following the diet prescribed and was reported seizure-free to date. **Patient n°3** remained seizure-free for 3 weeks following a ketogenic diet and was still under observation when the paper was published. Wilder could not elaborate conclusions as there were only three patients, but this report represents a method of observing the effect of ketosis on patients with epilepsy. If ketosis caused the beneficial effect of fasting, it may be possible to substitute fasting for a ketogenic dietary therapy, which patients could easily follow and continue at home as long as required.
Weeks et al. (1923) Observations on fasting and diets in the treatment of epilepsy, *Journal of Metabolic Research*, 3:317–364. United States of America	Three thousand patients with epilepsy were registered in 1923 in New Jersey; however, the authors estimated that it might only be a fraction of the real number in this state. Seventy-three individuals who represented various types and grades of epilepsy followed dietary treatments in the Epileptic Village. All the patients were classified as "mental defectives" in some manner or grades.	This investigation was carried out in the hospital of the Epileptic Village in Autumn 1921 to improve the condition of patients with epilepsy. Exercise was provided to the patients under the supervision of the staff. Staff also supervised the diet to avoid violations of the diet. Dietary therapies consisted in fasting, protein diet, carbohydrate diet, fat diet, high mixed rations diet, and nonnutritive bulk diet. Each patient went through 2 or 3 dietary regimes.	The authors first reviewed prior fasting experiences of Guelpa, Conklin, Geyelin, Goldbloom and Burr. The authors did not manage to analyze the urine of the 73 patients, but they did manage to analyze the occasional blood samples. No patient suffered from ordinary metabolic diseases (diabetes, nephritis, hypertension…). Wassermann reactions in blood and spinal fluid were negative except in 12 cases. All the 73 cases are individually described. **Fasting:** 49/73 patients were first changed from the regular mixed diet of the Village to complete fasting for 3 weeks, receiving only water, and 15/73 patients first received special weighed diets before 3 weeks of fasting. Weight loss was moderate (between 5 and 10 kg), probably because of the usual lack of activity of the patients. No harm resulted from the fasting. Plasma sugar was maintained at an even level. Acidosis was generally present but not severe. The nitroprusside reaction of the blood plasma was generally negative or faint. In few cases, moderate nitroprusside reactions appeared in the plasma, but the CO_2 capacity was usually not seriously reduced. In 2 cases, the reduction of the CO_2 capacity occurred below 40 vol%, but no clinical symptoms appeared; the fast was not stopped, and no treatment was needed. In 30/64 patients, seizures disappeared during the final 1 or 2 weeks of fasting, but it was interpreted as accidental by the authors. Maintenance of fasting did not always improve patients: in 6/64 patients who became seizure-free, seizures reappeared during the last days of the fast, and in 16/64 cases, fasting

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Table 1 (*continued*)

Summary of the patients' description, the methodology, and the results			
Article	Patients	Methodology	Results
			produced no change in seizures. Globally, a perceptible reduction in seizures was observed during the fasting. When fasting was stopped, seizures reappeared the same as before. Authors concluded that patients received no real benefit even during the fast. **Bulk diet:** 6/73 patients were changed from the regular Village diet to a nonnutritive bulk diet for 23 days. Patients received thin soup, agar jellies, thrice-cooked green vegetables, bran extracted with boiling water, celluflour, gum arable, mineral oil, petrolatum… This diet prevented intestinal rest. The loss of weight was slight (max 5 kg, and only 0.2 kg in 1 case). Plasma sugar fell slightly but was still normal. Acidosis was negligible. Changes were absent in 2/6 cases, doubtful in 1/6, and in 3/6, seizures were reduced as with fasting. The influence upon seizures was the same as with fasting. No harm resulted from this diet. **High protein diet:** 6/73 patients were transferred from the mixed Village diet to the highest protein rations for 48 days. Beginning with 110 g protein and 14 g fat, as a precaution against harm, rapidly increased to 260 g protein and 32 g fat. This diet consisted of clear soup, meat, fish, egg white, and casein (low in fat and free from carbohydrate). This diet is not irritating mechanically but furnishes a maximum of nitrogenous toxins (putrefactive intestinal flora). Patients were pleased with meats and casein cookies. All patients except 1 lost weight (undernutrition with no more than 1325 cal/day). Body strength was preserved better than in the fasting group. Plasma sugar did not change. Acidosis was absent. In 3/6 patients, seizures occurred less frequently during the experimental period than after. In other 3/6, seizures were more frequent during the experimental period than before. Results were variable, and the effects seemed to be accidental as with other diets. No harm resulted from this diet. **High calorie diet:** The 6/73 patients at the end of their nonnutritive bulk diet were changed to the largest quantities they could eat for 25 days in 5/6 and for 13 days in 1/6, which represented not less than 175 g protein, 530 g fat, 700 g carbohydrate, and 8000 cal. Indigestion and constipation were absent or easily controlled. Patients were very satisfied. Patients gained weight and body strength. Plasma sugar rose. Seizure frequency varied accidentally, and epilepsy did not worsen. **High carbohydrate diet:** 6/73 patients were transferred from the Village mixed diet to the highest possible carbohydrate for 24 days in 1/6 and for 48 days in 5/6. This diet consisted of corn starch, cane sugar, flour, cereals, and high carbohydrate vegetables and fruits, furnishing from 500 to 800 g carbohydrate/day. Proteins were usually no more than 11 g/day. Fat was absent or below 5 g/day. Changes in body weight were slight and variable. There was no reduction of strength. Acidosis was absent. Seizure frequency varied

Table 1 (*continued*)

Summary of the patients' description, the methodology, and the results			
Article	Patients	Methodology	Results
			accidentally. Absence of benefit. **High fat diet:** 6/73 patients were taken from the mixed Village diet and placed gradually on a high fat regime for 48 days (Sept 8–23: prot 15 g, fat 260 g, C.H. 2.5 g, cal 2410; Sept 24–Oct 1: prot 21 g, fat 250 g, C.H. 2.5 g, cal 2344; Oct 2–11: prot 21 g, fat 580 g, C.H. 3.7 g, cal 5318; Oct 12–26: prot 22 g, fat 440 g, C.H. 3.5 g, cal 4062). Good digestion. Only at the end, the appetite began to slightly weaken; thus, the fat had to be reduced for this reason. Weight changed very little, and strength and comfort were only slightly reduced. Acidosis was slight. Urine always showed positive nitroprusside reactions, but ferric chloride reaction remained negative in 2/6. At the end of the diet, 5/6 patients were placed on absolute fasting and showed no acidosis. Every patient gradually developed marked hyperglycemia (Benedict method, Folin–Wu method). Glycosuria was absent. Seizure frequency did not change.
Peterman (1924) The ketogenic diet in the treatment of epilepsy — A preliminary report, *The American Journal of Diseases of Children*, 28:28–33 United States of America	Eighty-six cases of epilepsy: 46 males and 40 females aged from 1 year to 15 years old (average age: 8.51 years). Average duration of symptoms noted by the parents was 3.3 years. Thirty patients had previous treatment. Twenty-two patients with "petit mal", 41 with "grand mal", and 23 with "grand and petit mal". Forty-three patients had a history of familial disease: 20 had a family history of migraine, 9 of epilepsy, and 14 of "insanity and nervousness". Twenty of 86 patients on ketogenic diet for a minimum of 2 months (13/20 diet alone, 7/20 diet with phenobarbital), 43/86 patients on 'routine treatment for epilepsy", 9/86 on anticonstipation diets and purging, 5/86 treated by other physicians, 9/86 on various treatments and not heard from.	To compare various treatments and present the ketogenic diet. Proteins must not exceed 1 g/kg of body weight in children. In adults, 2/3 of a g is adequate. The total calories should match the metabolic requirements of the patient, which can be calculated increasing the basal metabolism from 30 to 50%. The author cites these formulas to give the fat and carbohydrate: $F = 0.101\ M - 0.216\ P$; $C = 0.244\ M - 2.27\ F - P$. This should correspond to not more than 15 g of carbohydrate (sometimes less than 10 g) daily, with not more than 1 g of protein/kg of body weight and enough fat to obtain the required calories. The author estimates that these diets should not be started abruptly, but after a few days of a diet with less pronounced carbohydrate restriction.	Twenty of 86 patients on ketogenic diet for a minimum of 2 months: 13/20 diet alone and 7/20 diet with phenobarbital. Of the 13/20 patients with ketogenic diet alone, 9/13 were seizure-free for 2 months to 1 year (3 for 2 months, 1 for 3 months, 1 for 6 months, 1 for 8 months, 2 for 9 months, and 1 for 1 year), 4/9 of these patients had "petit mal", 3/9 "grand mal", and 2/9 both "grand and petit mal". Two of 13 patients with only occasional seizures showed improvement (1 with "petit mal", 1 with both "grand and petit mal"). One of 13 patients, with "grand and petit mal", did not show improvement. The author does not have the results of 1/13 patient. Of the 4/7 patients with ketogenic diet and phenobarbital, 1 with "grand mal" became seizure-free and 2 with "grand mal" and 1 with "grand and petit mal" had only occasional attacks. The author does not have the results of 1/7 patient. Three of 7 patients quit the diet and reported no change in their seizures. From 17 patients treated with a ketogenic diet (with or without phenobarbital), 10/17 are seizure-free (9/10 treated with the diet alone), 4/17 showed improvement, 2/17 were not heard from, and 1/17 patient still on the diet did not show improvement. Patients with "petit mal" (which does not respond so well to phenobarbital) showed more improvement. The author compared the ketogenic diet with other treatments, such as the "*routine treatment for epilepsy*" applied to 43/86 patients and which consisted in removing of all foci of infection, improving daily life (avoid excitement and mental strain, rest, daily bowel movement, anticonstipation diet), correcting errors of refraction, and taking phenobarbital and/or sodium bromide. Idiopathic and symptomatic epilepsy are not distinguished regarding treatment, except for focal convulsions following injury. With this "routine treatment", 15/43 patients (10 with "grand mal", 2 with "petit mal", and 3 with

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Table 1 (*continued*)

Summary of the patients' description, the methodology, and the results			
Article	Patients	Methodology	Results
			"grand and petit mal") were seizure-free for 6 months to 3 years, 7/43 (3 with "grand mal", 2 with "petit mal", and 2 with "grand and petit mal") were improved with only occasional seizures, 11/43 patients did not show improvement, and 10/43 were not heard from. Three of 86 patients (1 with "grand mal", 1 with "petit mal", and 1 with both) were seizure-free with anticonstipation diets and purging only; meanwhile, 6/86 patients (5 with "grand mal", and 1 with "petit mal") did not show any improvement. Five of 86 patients were treated by other physicians with various results. Nine of 86 patients following various treatments were not heard from. Five illustrative cases (3 boys, 2 girls, aged from 8 years to 11 years and 7 months) of patients with epilepsy (4 with "petit mal", 1 with "grand mal") cured with ketogenic diet are also given.
Peterman (1925) The ketogenic diet in epilepsy, *JAMA*, 84:1979–1983 United States of America	Thirty-seven children with essential or idiopathic epilepsy who followed the ketogenic diet at home were observed during 4 months to 2 and a half years. Twenty boys and 17 girls aged from 2 1/4 to 14 1/2 years (median average 8 6/10 years). Seven of 37 patients had "grand mal", 17/37 "petit mal", and 13/37 both "grand and petit mal". Nineteen of 37 cases with familial disease, 10/37 with migraine, 3/37 with epilepsy, 3/37 with "nervousness", and 3/37 with syphilis. Duration of symptoms is from 2 weeks to 7 years (median average duration 2.3 years). Seizure frequencies are from 1 "grand mal" every 5 months to 10 daily and from 3 "petit mal" a week to 200 daily. Seizures increased in number or severity or both in 28/37 cases. Stationary disease in 9/37.	To observe the effects of the ketogenic diet on patients with epilepsy. Every patient treated with the ketogenic diet followed an individual prescription to produce ketosis measured by acetone and diacetic acid in the urine. The basal metabolic requirement is determined or calculated thanks to the Dû Bois normal standards that depend on the age, weight, and height, and 30% is added for growth and energy (it will approximate 77 cal/kg). After a few days of gradual carbohydrate restriction (50, 40, or 20 g/day) with increasing fat (70, 90, or 100 g/day), the patient will follow his individual prescription (10 to 15 g of carbohydrate/day, 1 g of protein/kg of body weight, and sufficient fat for the metabolic requirement) with the addition of vitamins and salts. Water is not restricted. If the diet is started gradually, it is well tolerated.	Epileptic seizures usually stopped with the ketogenic diet when the ketosis is obtained. It was sometimes necessary to decrease the carbohydrate or to increase the fat, or both, for seizures to stop. In 1 case, the ratio of 7 g of fat to 1 g of combined carbohydrate and protein was used, and no harm was observed with these high fat ratios. During the preliminary carbohydrate restriction, some patients suffered from nausea and vomiting, which was quickly relieved by orange juice. Several patients did not show improvement with the ketogenic diet after 4 to 8 weeks. They were then put on fasting for 1 week and then again to the ketogenic diet, after which seizures stopped. Patients usually remained at the Mayo Clinic for 2 or 3 weeks or until they were seizure-free and their parents could manage the diet, which could be adjusted by correspondence. When the patients were seizure-free for 3 to 4 months showing ketonuria, diets were gradually changed according to the patient reactions. Carbohydrate was increased 5 g every other month, alternating with an increase of 5 g of protein. Fat was decreased or increased regarding the body weight. If the patient was seizure-free for weeks, and seizures occurred again, the diet was checked and usually, other sources of food or errors in calculation were found. If there was no break in the diet, fat was increased until seizures stopped. Three cases illustrate the response to the high fat diet. Two boys and 1 girl, aged from 5 1/2 years to 13 years, 1 with "grand mal and petit mal", 1 with "petit mal", and 1 with "grand mal". They were seizure-free for 13 months, 7 months, and 2 1/2 years. Nineteen of 37 patients were seizure-free with the ketogenic diet: 8/19 from 1 to 2 1/2 years and 11/19 from 3 months to 1 year. Several patients were seizure-free from 1 to 8 months when diet breaks caused 1 or more seizures. Purging and resumption of the diet immediately

Table 1 (*continued*)

Summary of the patients' description, the methodology, and the results			
Article	Patients	Methodology	Results
			controlled the seizures. Thirteen of 37 patients showed improvement, and 12/13 were still undergoing adjustment of the diet. Three of 37 patients were seizure-free from 3 to 8 months but were not heard from after that. One of 37 did not show improvement. One of 37 was seizure-free only 2 weeks ago when the paper was written. All 37 patients showed normal development (mentally, growth…). All patients improved their character: less irritability, increased interest and alertness, and better sleep and discipline. Five of 37 patients suffered from severe infections (scarlatina, pertussis, acute upper respiratory infection) with normal convalescence and no alteration of the diets during illnesses. Three of 37 went back to normal diets after 9, 12, and 12 months of treatment and were still seizure-free. A dose of half the amount necessary of phenobarbital on normal diet was also administered to 2/37 with the ketogenic diet.
Talbot et al. (1927) Epilepsy: chemical investigations of rational treatment by production of ketosis, *The American Journal of Diseases of Children*, 33:218–225 United States of America	Several cohorts of children are presented in this article without always providing the number of patients. One cohort consisted in 24 children with epilepsy under fasting. Ten of 24 were studied chemically. Cases 9 and 10 are reported in this article.	To study the difference between fasting and ketogenic diet.	Convulsive seizures stopped in 24/24 children during fasting because of ketosis. During fasting, blood uric acid concentration increased, blood sugar decreased, blood pH slightly decreased, carbon dioxide combining power decreased and, a marked excretion of acetone bodies occurred that can be observed in the breath and urine. There was no change in the blood nonprotein nitrogen and amino acids. After fasting, there was a temporary cessation of seizures, but in all cases, epilepsy recurred. The ketogenic diet obtained the same chemical changes as fasting and could be maintained more than a few days. A series of children (exact number is not known) with epilepsy followed a ketogenic diet and were studied during 2 years. As the carbohydrate was reduced and the fat was increased in the food, the production of acetone in the blood increased and the sugar in the blood decreased. In fasting children, the blood sugar was between 50 and 70 mg/100 ml, while in children on a ketogenic diet, it was between 60 and 80 mg/100 ml. In fasting children, the carbon dioxide combining power of the blood was between 35 and 45% by volume, while on a ketogenic diet, it was between 40 and 50% by volume. The blood uric acid was similar in fasting children and in children on a ketogenic diet. There was no change in the nonprotein nitrogen, phosphorus, calcium, or chlorides. The increase of the ketogenic ratio increased the excretion of acetone, which could be measured with acetone and diacetic acid tests of the urine and acetone test of the breath. It was a good index as to whether the diet was being followed or not. On the higher ketogenic diets applied at home, the excretion of acetone bodies varied between 2 and 6 g. The addition of carbohydrates to the diet caused the disappearance of the acetone in the urine, breath, and blood. Twenty-four

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Table 1 (*continued*)

Summary of the patients' description, the methodology, and the results			
Article	Patients	Methodology	Results
Talbot et al. (1927) A clinical study of epileptic children treated by ketogenic diet, *Boston Medical and Surgical Journal*, 196:89–96 United States of America	Twelve cases with epileptiform convulsions of unknown etiology treated in the Outpatient Clinic of the Massachusetts General Hospital, on the ward and in private practice, with no birth injury, normal physical examination, no abnormal neurological findings, normal psychometric test, negative blood Wassermann test, normal skull, and normal gastrointestinal tract. Cooperation of the child and the parents was required.	To discuss on the ketogenic diet used in the Outpatient Clinic of the Massachusetts General Hospital and its fulfillment of the needs of the patients, and to observe the beneficial results of a dietary treatment applied to children with epilepsy.	to 48 h after the change to an ordinary diet, the excessive amounts of acetone disappeared from the urine, breath, and blood. Ketones also disappeared and seizures recurred. Similar chemical changes occurred in children with epilepsy treated by fasting and by ketogenic diet. A marked production of ketones (increased blood acetone concentration, marked excretion of acetone bodies in the breath and in the urine) was observed in patients treated by fasting and ketogenic diet. The alkaline reserve (carbon dioxide combining power) was lowered and a decrease in the blood sugar concentration was observed. When a pronounced ketosis is produced by a special diet, seizures in children usually decrease in number or disappear. All ketogenic diets must contain an excess of ketone-forming foods, which results in a large excretion of ketone bodies. The diet should be complete in total calories, protein, vitamins, and salts. The total caloric requirement depends on height, weight, physical characteristics, and the mode of life. Fifty percent caloric needs should be added to the basal needs. The protein requirements vary from 11/2 to 2 g/kg of body weight in infants to 2–6/10 and 4 g in older children (the amount of protein should be kept as low as possible). The physical development of these children was normal. In no instance the children became weaker. The vitamins and the mineral requirements were sufficiently supplied in this diet. There was no restriction of salt intake. With this diet, a marked ketosis was expected that could be measured with the test for acetone in the breath by the Scott Wilson solution, by the large amounts of acetone excreted in the urine, and by the large amounts of acetone in the blood. A marked ketosis could be maintained without causing any unwanted symptoms. These patients could fight mild infections even with a marked ketosis. The health of these children even improved during ketosis as they seemed to be more free from infections than the other members of their family. This could be explained by the fact that patients are required to drink plenty of water, to have a rest hour when possible, and to go to bed early. The bran in the diet fought constipation, and noncarbohydrate cathartics could be given when needed. With the diet, patients showed increased alertness, diminished nervousness and excitability, and improvement in their complexions. One patient had slight nausea: a more appetizing arrangement of the diet stopped it. The formula the authors used for the ketogenic diet is then explained. During the early study of effects of a ketogenic diet on children with epilepsy, the type of cases treated were limited: 1 patient with convulsions and a history of birth injury was benefited by the diet; 1 with “grand mal”, “mentally retarded”, became “normal mentally” since her seizures were stopped by diet; 1 suffered from chorea and frequent “petit mal”,

Table 1 (*continued*)

Summary of the patients' description, the methodology, and the results			
Article	Patients	Methodology	Results
			which both disappeared 2 weeks after starting the diet. A ketogenic diet with marked ketonuria improving the epileptic symptoms was not attained in the majority of the cases until a 3:1 diet was established. A hospital residence of a couple of weeks is better to establish the diet. One patient with 50 attacks/day was given a diet in the hospital restricted in carbohydrate and increased in fat producing a marked ketosis. When her diet ratio was 3:1, her seizures dropped to 6/day. With higher ratios, she became seizure-free. After that, she was given a normal diet, high in carbohydrate and low in fat; her seizures recurred 12 h before the first normal blood sugar at their usual rate. This suggested that the freedom from seizures could be due to hypoglycemia, but the authors concluded that "after 3 months study of insulin therapy in the treatment of epilepsy it was found impractical". Another patient, after 17 days of a ketogenic diet (3:1), showed a drop in her blood CO_2 combining power from 53.3 to 45.2 vol%, a drop in her blood sugar from 99 to 67 mg/100 ml, and an increase in her blood acetone to 0.450 g/l. She had 15 seizures/day before starting the diet. She was seizure-free for 9 weeks on a 3:1 diet. Ten of 12 patients were seizure-free on ketogenic diet for 7 weeks to 9 months, 1/12 showed a decrease of the frequency and severity of seizures, and 1/12 still presented convulsions but followed the diet poorly.
Helmholz (1927) The treatment of epilepsy in childhood — Five year's experience with the ketogenic diet, *JAMA*, 88:2028–2032 United States of America	One hundred and forty-four patients with epilepsy treated with ketogenic diet: 12/144 with symptomatic epilepsy complicating encephalitis (n = 6) or cerebral palsy (n = 6) and 132/144 with idiopathic epilepsy.	To study the impact of the ketogenic diet on patients with epilepsy. Treatment failures are determined as all patients in which there was no definite improvement after 2 months or more of the ketogenic diet without adding medication.	Twelve patients presenting symptomatic epilepsy complicating encephalitis or cerebral palsy were treated with the ketogenic diet: 2/12 patients became seizure-free, 6/12 showed improvement (attacks less frequent and/or less severe, improvement of general condition), and 4/12 did not show any improvement. Seventeen of 132 patients with idiopathic epilepsy were not included in the result tables as they were only observed in the last six months. From those patients, 5/17 showed temporary improvement, 3/17 did not show any improvement, and it was not possible to conclude for 9/17 patients (attacks not frequent enough). From the 132 patients with idiopathic epilepsy, 24 patients' results were unclassified: either they were seizure-free for a long period and then suffered from a return of the attacks, either their state of ketosis was controversial, or either they required the administration of phenobarbital (luminal) to control the attacks. Ninety-one patients followed the ketogenic diet long enough to observe the effects of ketosis on convulsive seizures. Forty-two of 91 (46%) patients did not show any therapeutic effect of the diet. In 12/42, the degree of ketosis attained after the patient returned home is questionable. Only 30/42 patients presented frequently enough attacks to note the effects of ketosis: 14/30 were showed a temporary improvement, 12/30 did not show any improvement with the diet. Forty-nine of 91 patients (54%) showed definite improvement with the

(continued on next page)

Table 1 (*continued*)

Summary of the patients' description, the methodology, and the results			
Article	Patients	Methodology	Results
			diet: reduction of the number of attacks, lengthened intervals between attacks, and decrease of the severity of convulsions in "grand mal" attacks. In conclusion, 29/91 patients were seizure-free thanks to the ketogenic diet and 20/91 patients showed an improvement. The diet is hard to follow, and there are constant breaks in the diet. Ten patients became seizure-free when in a state of constant ketosis. Eight patients were seizure-free from 6 to 12 months, 3 patients were seizure-free for more than a year, and 18 patients were seizure-free from 1 to 4 years (12/18 ended on normal diet and were still seizure-free). In summary, the ketogenic diet freed 31% (46/144) of the patients from attacks and improved an additional 23% (34/144).
McQuarrie & Keith (1927) Epilepsy in children: Relationship of variations in the degree of ketonuria to occurrence of convulsions in epileptic children on ketogenic diets, *The American Journal of Diseases of Children*, 34:1013–1029 United States of America	Two patients with epilepsy treated with the ketogenic diet.	To determine the variations in the rate of excretion of the acetone bodies in urine and blood during one day to understand why some children with epilepsy benefited by a ketogenic diet continue to have occasional morning convulsions. When ketosis was established thanks to tests for acetone and aceto-acetic acid in the urine, samples were collected each 2 h 30 or 5 h day and night. Patients drank 100 ml of water at the beginning of each collection period. The colorimetric method of Behre and Benedict determined the acetone bodies in blood at different periods of the day. Sugar determinations were made at the same time because hypoglycemia may cause morning convulsions in children without epilepsy.	**D.S.** treatment was as follows: 3 days of fasting–>5 days of ketogenic diet–>1 week of high carbohydrate diet. She was seizure-free during this period, except for "petit mal" on the 3rd day of the carbohydrate diet. She was discharged from the hospital on a 1000 cal obesity diet (60 g each of protein and carbohydrate). She was seizure-free 2 months after discharge. **M.P.**: 24 h after admission, without treatment; she had 5 severe convulsive seizures. Opiates were given on the 2nd day and partly controlled the seizures. A diet with limited carbohydrates and as much fat as the patient would take was prescribed for 6 days and resulted in a marked ketosis after 3 days, the cessation of the convulsions, and improvement in the patient. After this, a diet consisting in 44 g of protein, 44 g of carbohydrate, and 252 g of fat was prescribed (fatty acid to glucose ratio of 1.7:1). Two days later, the ketosis decreased, and convulsions occurred every morning for 1 week until the diet was changed by a strongly ketogenic diet: 32 g of protein, 28 g of carbohydrate, and 200 g of fat (ratio of 2.9:1, fatty acid to glucose ratio of 2.4:1). Convulsions stopped after 36 h of this diet because after a series of seizures, the beneficial effect of ketosis is less marked (during the first 24 h, 2 mild seizures in the morning and 1 slight attack of "petit mal" in the evening). The authors confirmed that "*a definite relationship exists between the degree of ketosis and the occurrence of convulsions*". The diet was well followed for 10 days; seizures recurring only when the diet was not followed. For the 2 patients, the acetone body concentration in blood and urine evolved similarly. The blood sugar values remained normal in all subjects (with or without epilepsy). The rate of excretion of acetone bodies fluctuated during the day with the lowest rate in the morning and the highest in the late afternoon. The curve of excretion did not follow the curve of previous cases during the 90-h fasting period and the first 48 h of the ketogenic diet given after the fast. However, this changed on the 3rd day of the diet (low rates in the morning and high rates in the afternoon). With a high carbohydrate diet, there was no increase in the afternoon or

Table 1 (*continued*)

Summary of the patients' description, the methodology, and the results			
Article	Patients	Methodology	Results
			decrease in the morning in the rate of excretion. With a "*borderline diet*" (for example, protein 12 g, fat 60 g, carbohydrate 18 g for a 3-year-old child), there was a slight rise in the afternoon. The degree of ketosis required for the prevention of epileptic seizures is different for every patient, and even sometimes in the same patient. No harmful effects of the ketogenic diet have yet been reported. For children beyond 2 years, the protein requirement is not more than 1 g/kg of body weight. For a good degree of ketosis, carbohydrates must be less than 1 g/kg of body weight, especially in older children and in patients with severe epilepsy. The fat prescribed must be the amount required for the total energy requirement. For the authors, "*children up to 5 years old are allowed 1.25 g of protein and 0.75 g of carbohydrate per kg of body weight, those between 5 and 10 years are given 1 g of protein and 0.5 g of carbohydrate, while those above 10 years receive 1 g of protein and 0.25 g of carbohydrate per kg*". To provoke ketosis, the ketogenic to antiketogenic ratio is always above 3.2:1. In conclusion, the diet must be adjusted for each person regarding the degree of ketosis to prevent seizures, the total caloric value, the proteins and vitamins, and the digestibility and taste. The authors estimated that fasting before the ketogenic diet ensures its success.
Talbot (1927) The treatment of epilepsy of childhood by the ketogenic diet, *The Rhode Island Medical Journal*, 10:159–162 United States of America	Two hundred children with epilepsy from the Children's Clinic of the Massachusetts General Hospital, the Mayo Clinic, and a few in private practice.	To describe the ketogenic diet. Normal diet: proportions of ketogenic to antiketogenic foods are about 1:4. Before the ketogenic diet, patients were put on a 1 1/2:1 diet (increase in fat and decrease in carbohydrate) for 10 days to 2 weeks. The proportions were then changed to 2:1, 2 1/2:1, 3/1, 3 1/2:1, and 4:1 at 1 to 2 weeks intervals. The accuracy with which the diet was followed was checked up by tests for acetone in the urine every 24 h. In almost all patients, the diet had to be increased to 4:1 for the seizures to stopped. This could take 2 months. The patient was kept on the diet until he was seizure-free for 6 months. The diet was then gradually modified by increasing carbohydrate 10 g at a time and reducing the fat in corresponding amounts until the patient was on a normal diet with limited amount of carbohydrate. Candy and sweets were excluded from the final diet. A short period of fast could be employed to reinforce the effects of diet, but such a procedure should be avoided when possible. The fat and carbohydrate content of the diet could be calculated from this formula: Total Calories = 9XR(C + P) + 4C + 4P.	The ketogenic diet resulted in complete symptomatic relief in 33% of the 200 children with epilepsy and in definite improvement in 1/2 to 3/4 of the patients. Children with idiopathic epilepsy, cerebral palsy, and encephalitis showed improvement. Results were equally good in "petit mal" and "grand mal". Treatment was most effective when started in children before puberty, and there were more failures in patients in whom treatment was started later. A few adults were seizure-free. The general health of most of the patients on the diet improved. Constipation could be relieved by natural movements or with laxative free from sugar (plain granular agar-agar, mineral oils, diabetic or plain petrolagar, salts such as Carlsbad or Epsom, bitter fluid extract of Cascara). The excess of fat was well tolerated. Digestive symptoms could appear when the diet was changed too rapidly. One or 2 patients suffered from nausea during one day during the period of adjustment, but it was not necessary to stop the diet or give a treatment. One hour of rest per day should be taken. Two to 3 teaspoons of calcium lactate should be given daily with the meals to supplement the food calcium. Six to 8 glasses of water should be drunk daily. There was no restriction on salt. If the diet worked, luminal and bromides were not necessary and should be omitted in children. Adults could continue to use luminal and bromides, but they were encouraged to gradually reduce the dose.
Talbot (1928) The ketogenic diet in epilepsy, *Bulletin of the New York Academy of Medicine*, 4:401–408.	This paper is a review of different studies on ketogenic diet. No number of patients is given.	To review several studies on the use of the ketogenic diet with patients with epilepsy. No fasting preceded the modification of	The ketogenic diet conceived by Wilder had already been used during 6 years for patients with epilepsy when this paper

(*continued on next page*)

Table 1 (*continued*)

Summary of the patients' description, the methodology, and the results			
Article	Patients	Methodology	Results
United States of America		diet, but the change to one diet to the other was made gradually. Luther's working table was used to calculate the ketogenic–antiketogenic ratio. It was recommended to modify the diet from normal to 1 1/2:1, and then to follow the sequence of 2:1, 2 1/2:1, 3:1, 3 1/2:1, and 4:1. If ketosis needed to be induced quickly or when the patient had a "very strong digestion", some steps could be omitted. The response to the diet was determined by chemical tests and varied between individuals. Acetone in breath (Higgin's method) confirmed early ketosis and could appear with the ratio 1 1/2:1. When the ratio of the diet became 2:1; the sodium nitroprusside test in the urine could become positive, and the ferric chloride test remained negative until 2 1/2:1. The number of calories administered should be 50%+ than the basal caloric requirement (for physically active children, it must be more than for children doing little exercise). One gram of protein/kg of body weight should be given to children before marked ketosis.	was published. Thirty-three percent of all children treated became seizure-free. The proportion of seizure-free adults was smaller. The effectiveness of the diet depends in part on its adjustment: the percentage of children seizure-free in the Research Ward of the Massachusetts General Hospital, similar to those published by Peterman and Helmholz, was twice that found in the usual clinic. The percentage of seizure-free children was even higher in private practice, probably due to the more attention and care in private clinics than larger clinics. Epilepsy improvement with fasting and ketogenic diet was associated with acidosis, ketosis, lowering of sugar content of the blood, and diminution of the alkaline reserve. No explanation for the effectiveness of the treatment was found at that time. Marked ketosis for months did not affect the general health and improved patients with epilepsy: susceptibility to infections was reduced and resistance to sicknesses was raised. Children continued to grow and gain weight normally. The change from a normal to a ketogenic diet should not be abrupt in order to avoid abdominal discomfort, nausea, and symptoms of indigestion. Usual normal ketogenic–antiketogenic ratio was 1:4. During ketosis, a positive protein balance was not maintained in children more than 8 or 10 years old until the intake was about 1 1/4 g/kg of expected body weight, which showed that more proteins should be given in the diet and that the balance should be determined from time to time during treatment. Ketosis increased the calcium excretion. Small doses of calcium lactate (2–3 g/day) should thus be given during ketosis.

2. Materials and methods

Wilder's first paper "*The effects of ketonemia on the course of epilepsy*" published on July 27, 1921 in *The Clinic Bulletin* was found in the library of the French Pasteur Institute. Wilder's second article "*High fat diets in epilepsy*" published consecutively the next day on July 28, 1921 in *The Clinic Bulletin* was provided by Professor Eric Kossoff. Then, we carried out a literature review of articles on KD and epilepsy published in the 1920s.

We read and analyzed those articles. We have summarized in the Results section below the patients' characteristics, the methodology, and the results of those papers. A detailed description of those articles is also available in Table 1.

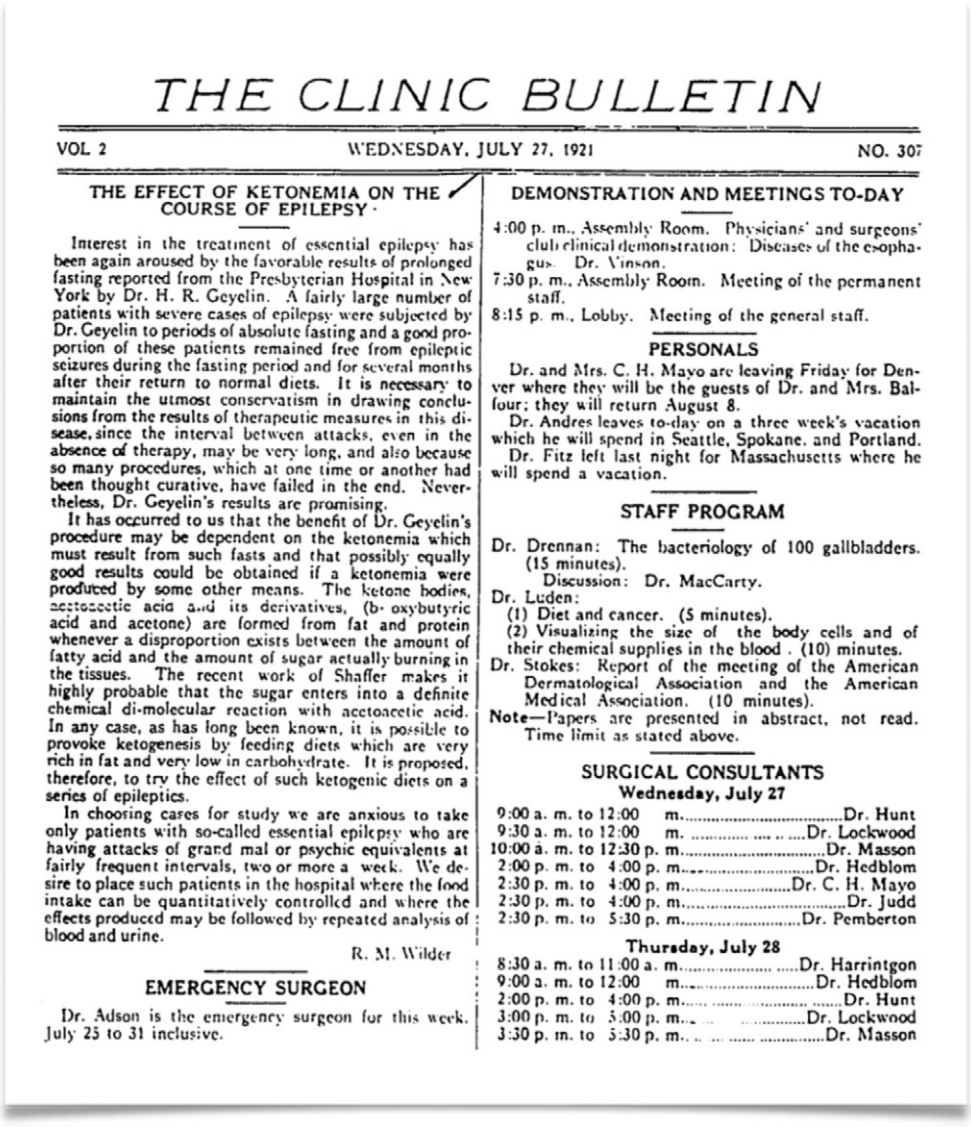
3. Results

In addition to the two Wilder papers from 1921, we found 9 papers on KD published during the 1920s. During this period, KD was studied on more than 400 patients with epilepsy (approximately 421 patients; precise numbers of patients are sometimes hard to find). We will detail these articles below.

3.1. Wilder papers on ketogenic diet

In his first paper published in 1921, Wilder reported on the interest of fasting in the treatment of epilepsy [9], referring to the results obtained with fasting at the Presbyterian Hospital, New York, by Dr. H. R. Geyelin [14]. Dr. Geyelin subjected 26 patients with epilepsy aged from 3 to 35 years to periods of absolute fasting. After ten days of fast, only 4/26 patients still presented seizures. Two of 26 patients remained seizure-free for 1 year or over a year, 6/26 patients treated by one or two fasts did not show any improvement, and 18/26 patients showed marked improvement. A good proportion of patients remained free from seizures during the fasting period and for several months after their return to normal diets. With these results, Wilder suggested that the benefits of fasting on seizures might be dependent on ketonemia [9] (Fig. 1). He then hypothesized that possibly equally good results could be obtained with a KD, very rich in fat and very low in carbohydrate, which would provoke ketogenesis [9] (Fig. 1). He proposed to observe the effects of this diet that could be maintained for a longer period than fasting.

In his second paper, a KD was followed for the first time by three patients with epilepsy in the Mayo Clinic [10] (Fig. 2). A boy aged 13 years with '*epilepsy–migraine syndrome*' with 2 to 3 seizures per week followed a KD (15 g of carbohydrate, 57 g of protein, and 231 g of fat),



THE CLINIC BULLETIN

VOL 2 WEDNESDAY, JULY 27, 1921 NO. 307

THE EFFECT OF KETONEMIA ON THE COURSE OF EPILEPSY

Interest in the treatment of essential epilepsy has been again aroused by the favorable results of prolonged fasting reported from the Presbyterian Hospital in New York by Dr. H. R. Geyelin. A fairly large number of patients with severe cases of epilepsy were subjected by Dr. Geyelin to periods of absolute fasting and a good proportion of these patients remained free from epileptic seizures during the fasting period and for several months after their return to normal diets. It is necessary to maintain the utmost conservatism in drawing conclusions from the results of therapeutic measures in this disease, since the interval between attacks, even in the absence of therapy, may be very long, and also because so many procedures, which at one time or another had been thought curative, have failed in the end. Nevertheless, Dr. Geyelin's results are promising.

It has occurred to us that the benefit of Dr. Geyelin's procedure may be dependent on the ketonemia which must result from such fasts and that possibly equally good results could be obtained if a ketonemia were produced by some other means. The ketone bodies, acetoacetic acid and its derivatives, (b- oxybutyric acid and acetone) are formed from fat and protein whenever a disproportion exists between the amount of fatty acid and the amount of sugar actually burning in the tissues. The recent work of Shaffer makes it highly probable that the sugar enters into a definite chemical di-molecular reaction with acetoacetic acid. In any case, as has long been known, it is possible to provoke ketogenesis by feeding diets which are very rich in fat and very low in carbohydrate. It is proposed, therefore, to try the effect of such ketogenic diets on a series of epileptics.

In choosing cases for study we are anxious to take only patients with so-called essential epilepsy who are having attacks of grand mal or psychic equivalents at fairly frequent intervals, two or more a week. We desire to place such patients in the hospital where the food intake can be quantitatively controlled and where the effects produced may be followed by repeated analysis of blood and urine.

R. M. Wilder

EMERGENCY SURGEON

Dr. Adson is the emergency surgeon for this week, July 25 to 31 inclusive.

DEMONSTRATION AND MEETINGS TO-DAY

4:00 p. m., Assembly Room. Physicians' and surgeons' club clinical demonstration: Diseases of the esophagus. Dr. Vinson.
7:30 p. m., Assembly Room. Meeting of the permanent staff.
8:15 p. m., Lobby. Meeting of the general staff.

PERSONALS

Dr. and Mrs. C. H. Mayo are leaving Friday for Denver where they will be the guests of Dr. and Mrs. Balfour; they will return August 8.

Dr. Andres leaves to-day on a three week's vacation which he will spend in Seattle, Spokane, and Portland.

Dr. Fitz left last night for Massachusetts where he will spend a vacation.

STAFF PROGRAM

Dr. Drennan: The bacteriology of 100 gallbladders. (15 minutes).
Discussion: Dr. MacCarty.
Dr. Luden:
(1) Diet and cancer. (5 minutes).
(2) Visualizing the size of the body cells and of their chemical supplies in the blood. (10) minutes.
Dr. Stokes: Report of the meeting of the American Dermatological Association and the American Medical Association. (10 minutes).
Note—Papers are presented in abstract, not read. Time limit as stated above.

SURGICAL CONSULTANTS

Wednesday, July 27

9:00 a. m. to 12:00 m. ..... Dr. Hunt
9:30 a. m. to 12:00 m. ..... Dr. Lockwood
10:00 a. m. to 12:30 p. m. ..... Dr. Masson
2:00 p. m. to 4:00 p. m. ..... Dr. Hedblom
2:30 p. m. to 4:00 p. m. ..... Dr. C. H. Mayo
2:30 p. m. to 4:00 p. m. ..... Dr. Judd
2:30 p. m. to 5:30 p. m. ..... Dr. Pemberton

Thursday, July 28

8:30 a. m. to 11:00 a. m. ..... Dr. Harrintgon
9:00 a. m. to 12:00 m. ..... Dr. Hedblom
2:00 p. m. to 4:00 p. m. ..... Dr. Hunt
3:00 p. m. to 5:00 p. m. ..... Dr. Lockwood
3:30 p. m. to 5:30 p. m. ..... Dr. Masson

Fig. 1. Wilder published his first article '*The effect of ketonemia on the course of epilepsy*' in *The Clinic Bulletin* journal in 1921 on July 27th.

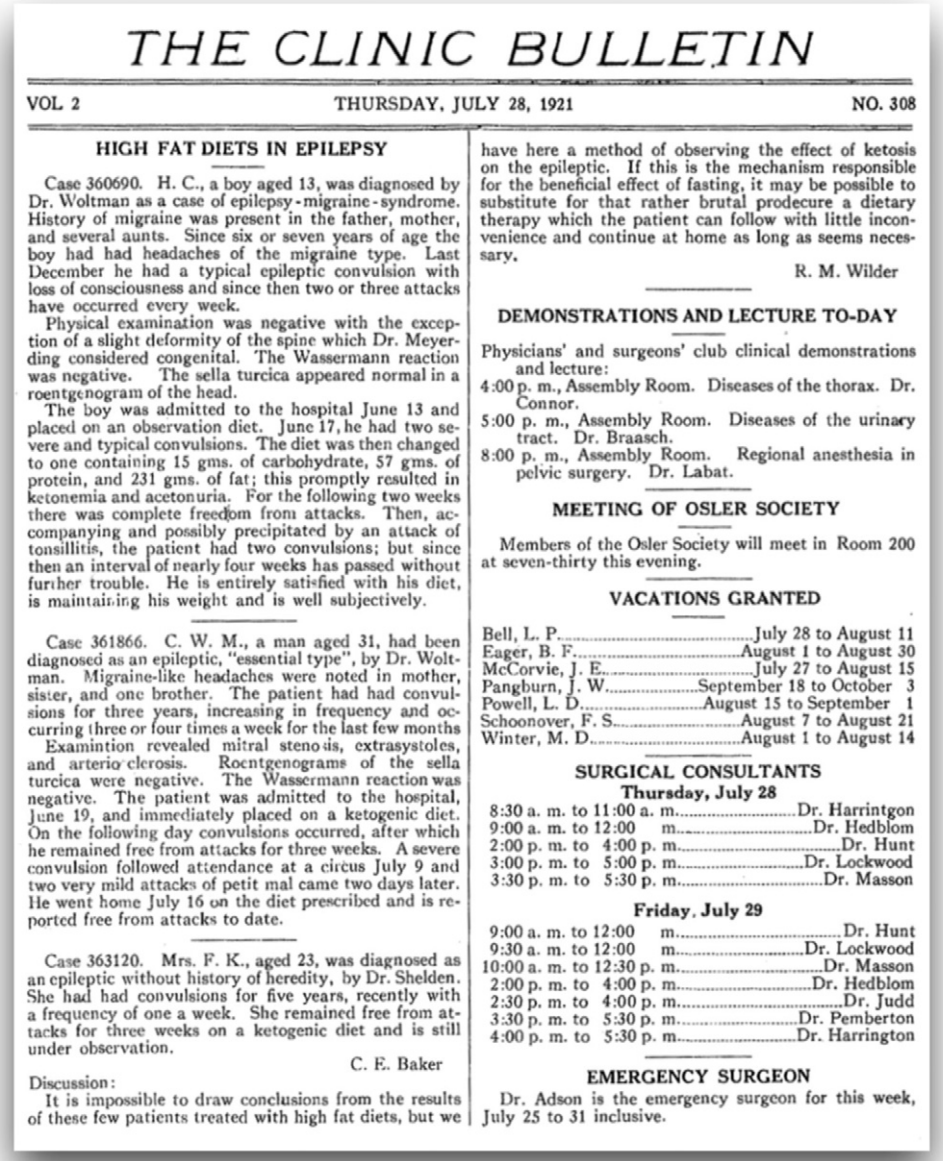
which quickly resulted in ketonemia and acetonuria. He was seizure-free during 2 weeks. Then, the patient experienced 2 convulsions during an acute tonsillitis, but after that, nearly 4 weeks passed without any seizures. The second patient was a man aged 31 years with '*essential type epilepsy*'. On the following day of his admission to the hospital and the start of the KD, seizures occurred, after which he remained free from seizures for 3 weeks. Then, a '*severe seizure*' and 2 very mild seizures occurred. Thereafter, he was reported seizure-free for almost two weeks at the time of the publication of this first report. The third patient was a woman aged 23 years who had epilepsy for the last five years with one seizure per week. She remained seizure-free for 3 weeks on a KD and was still under observation when the paper was published.

3.2. Studies of 1920s on ketogenic diet

In order to understand how the use of KDT spread after the publication of the first two Wilder papers, we conducted a bibliographic search for papers on KD published during the 1920s. We summarized the data of these papers below.

In 1923, Weeks et al. published a study on dietary treatments on 73 patients with epilepsy gathered in the State Village for Epileptics in Skillman, New Jersey [15]. This study was mostly conducted in the hospital of the 'Epileptic Village'. Various types and grades of epilepsy were represented. In addition to fasting (46 patients during 3 weeks), patients went through dietary regimes, which consisted in nonnutritive bulk diet for 23 days (6 patients), high protein diet for 48 days (260 g protein, 32 g fat in 6 patients), high calorie diet for at most 25 days (not less than 175 g protein, 530 g fat, 700 g carbohydrate, and over 8000 cal in 6 patients), high carbohydrate diet for at most 48 days (from 500 to 800 g carbohydrate daily, from 11 to 37 g of protein daily, no fat or below 5 g/day in 6 patients), and high fat diet for 48 days (from 15 to 22 g of protein, from 250 to 580 g of fat, from 2.5 to 3.7 g of carbohydrate, from 2344 to 5318 cal in 6 patients). The authors stated that glycosuria was absent and that acidosis was slight. They also mentioned that the patients developed hyperglycemia, assuming that it was related to the high fat diet regime. Weeks et al. concluded that in general, the patients did not seem to benefit of any of these dietary treatments, even during fasting, although a perceptible reduction in seizures appeared during the fasting period.

Following this publication, in 1924 and 1925, Peterman compared KDs with other treatments [16,17]. Peterman's KD was composed of 1 g of protein/kg of body weight in children, from 10 to 15 g of carbohydrate per day, and the remainder of the calories in fat, which is similar to



THE CLINIC BULLETIN

VOL 2 THURSDAY, JULY 28, 1921 NO. 308

HIGH FAT DIETS IN EPILEPSY

Case 360690. H. C., a boy aged 13, was diagnosed by Dr. Woltman as a case of epilepsy-migraine-syndrome. History of migraine was present in the father, mother, and several aunts. Since six or seven years of age the boy had had headaches of the migraine type. Last December he had a typical epileptic convulsion with loss of consciousness and since then two or three attacks have occurred every week.

Physical examination was negative with the exception of a slight deformity of the spine which Dr. Meyerding considered congenital. The Wassermann reaction was negative. The sella turcica appeared normal in a roentgenogram of the head.

The boy was admitted to the hospital June 13 and placed on an observation diet. June 17, he had two severe and typical convulsions. The diet was then changed to one containing 15 gms. of carbohydrate, 57 gms. of protein, and 231 gms. of fat; this promptly resulted in ketonemia and acetonuria. For the following two weeks there was complete freedom from attacks. Then, accompanying and possibly precipitated by an attack of tonsillitis, the patient had two convulsions; but since then an interval of nearly four weeks has passed without further trouble. He is entirely satisfied with his diet, is maintaining his weight and is well subjectively.

Case 361866. C. W. M., a man aged 31, had been diagnosed as an epileptic, "essential type", by Dr. Woltman. Migraine-like headaches were noted in mother, sister, and one brother. The patient had had convulsions for three years, increasing in frequency and occurring three or four times a week for the last few months

Examintion revealed mitral stenosis, extrasystoles, and arterio clerosis. Roentgenograms of the sella turcica were negative. The Wassermann reaction was negative. The patient was admitted to the hospital, June 19, and immediately placed on a ketogenic diet. On the following day convulsions occurred, after which he remained free from attacks for three weeks. A severe convulsion followed attendance at a circus July 9 and two very mild attacks of petit mal came two days later. He went home July 16 on the diet prescribed and is reported free from attacks to date.

Case 363120. Mrs. F. K., aged 23, was diagnosed as an epileptic without history of heredity, by Dr. Shelden. She had had convulsions for five years, recently with a frequency of one a week. She remained free from attacks for three weeks on a ketogenic diet and is still under observation.

C. E. Baker

Discussion:

It is impossible to draw conclusions from the results of these few patients treated with high fat diets, but we have here a method of observing the effect of ketosis on the epileptic. If this is the mechanism responsible for the beneficial effect of fasting, it may be possible to substitute for that rather brutal prodecure a dietary therapy which the patient can follow with little inconvenience and continue at home as long as seems necessary.

R. M. Wilder

DEMONSTRATIONS AND LECTURE TO-DAY

Physicians' and surgeons' club clinical demonstrations and lecture:

4:00 p. m., Assembly Room. Diseases of the thorax. Dr. Connor.

5:00 p. m., Assembly Room. Diseases of the urinary tract. Dr. Braasch.

8:00 p. m., Assembly Room. Regional anesthesia in pelvic surgery. Dr. Labat.

MEETING OF OSLER SOCIETY

Members of the Osler Society will meet in Room 200 at seven-thirty this evening.

VACATIONS GRANTED

Bell, L. P.	July 28 to August 11
Eager, B. F.	August 1 to August 30
McCorvie, J. E.	July 27 to August 15
Pangburn, J. W.	September 18 to October 3
Powell, L. D.	August 15 to September 1
Schoonover, F. S.	August 7 to August 21
Winter, M. D.	August 1 to August 14

SURGICAL CONSULTANTS

Thursday, July 28

8:30 a. m. to 11:00 a. m.	Dr. Harrintgon
9:00 a. m. to 12:00 m.	Dr. Hedblom
2:00 p. m. to 4:00 p. m.	Dr. Hunt
3:00 p. m. to 5:00 p. m.	Dr. Lockwood
3:30 p. m. to 5:30 p. m.	Dr. Masson

Friday, July 29

9:00 a. m. to 12:00 m.	Dr. Hunt
9:30 a. m. to 12:00 m.	Dr. Lockwood
10:00 a. m. to 12:30 p. m.	Dr. Masson
2:00 p. m. to 4:00 p. m.	Dr. Hedblom
2:30 p. m. to 4:00 p. m.	Dr. Judd
3:30 p. m. to 5:30 p. m.	Dr. Pemberton
4:00 p. m. to 5:30 p. m.	Dr. Harrington

EMERGENCY SURGEON

Dr. Adson is the emergency surgeon for this week, July 25 to 31 inclusive.

Fig. 2. Wilder published his second article '*High fat diets in epilepsy*' in *The Clinic Bulletin* journal in 1921 on July 28th.

the KD used nowadays. In the first paper, 20 patients followed a KD for not less than 2 months (13/20 only KD, 7/20 KD with phenobarbital). Of the 13/20 patients with KD alone, 9/13 were free from further attacks for 2 months to 1 year. Three patients abandoned the diet and reported no change. Of the 17 patients treated with a KD (with or without phenobarbital), 10/17 were entirely free from convulsions (9/10 treated with the diet alone), 4/17 showed improvement, 2/17 had not been heard from, and 1/17 patient did not respond to the diet [16]. In his second study, 19/37 patients became free from seizures with the KD (8/19 free from convulsions from 1 to 2 years and 11/19 from 3 months to 1 year). Peterman also observed that excessive ketosis provoked symptoms such as nausea or vomiting, which could be relieved by orange juice [17]. We do not know if the patients studied in the second paper of Peterman are partially the same as in his first paper published in 1924. Peterman also reported the effect of the KD on the comorbidities mentioning an improvement in all patients with less irritability and improved alertness (Table 1) [17].

These reports were quickly followed by other publications from Talbot in 1927 and 1928, Helmholz in 1927, and McQuarrie & Keith also in 1927. Talbot first realized a study on 200 children with epilepsy from the Children's Clinic of the Massachusetts General Hospital, the Mayo Clinic, and private practice [18]. The KD (4:1) resulted in complete symptomatic relief in 33% of the 200 children with epilepsy, and it was followed with definitive improvement in nearly three-quarters of the patients. A second paper published this same year by Talbot et al. aimed to compare fasting with KD [19]. Blood chemical studies of cohorts of children with epilepsy treated by fasting and by KD showed similar chemical changes. The exact number of patients is not clearly stated. Patients treated by both methods showed a marked production of ketones as evidenced by an increased blood acetone concentration and by a marked excretion of acetone bodies in the breath and in the urine. The alkaline reserve as measured by the carbon dioxide combining power was lowered, and there was a decrease in the blood sugar concentration. The ketosis caused by fasting and by KD was associated

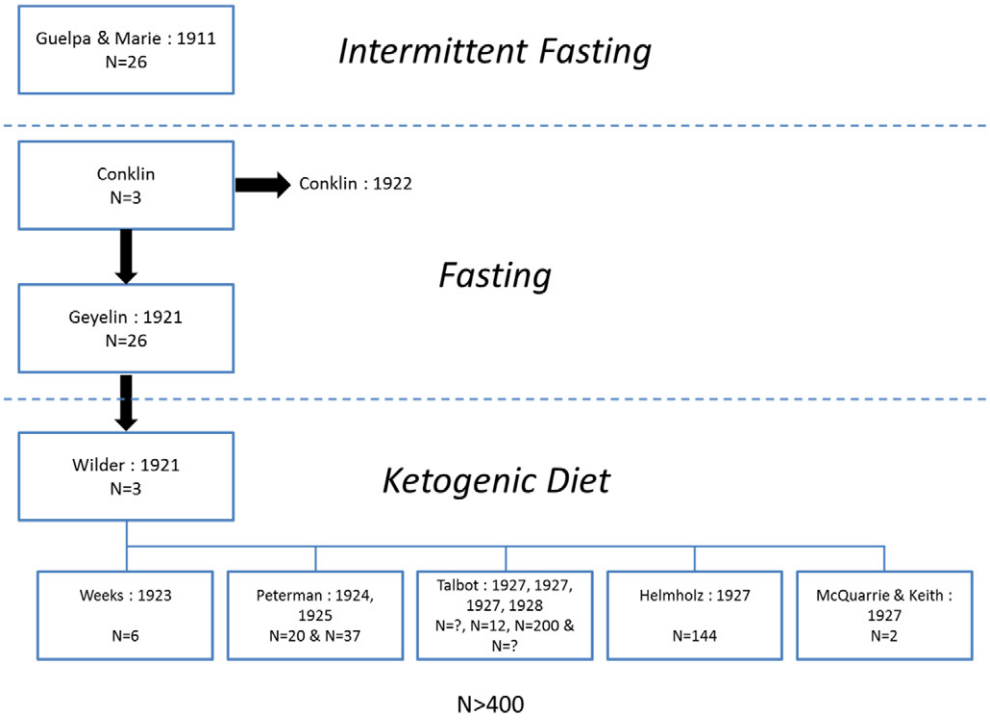


Fig. 3. History of the use of ketogenic diet for patients with epilepsy in the 1920s. The papers are classified by type of diet. We reported the number of patients from each paper in each box with the name of the author and the year of publication.

with a diminution or cessation of attacks. In another article from 1927, Talbot showed the beneficial results of KD applied to 12 patients with epilepsy, concluding that a diet sufficiently ketogenic to produce a marked ketonuria usually resulted in a definite improvement of epileptic symptoms: 10/12 patients did not have seizures under KD for 7 weeks to 9 months, 1 patient showed a diminution of the frequency and severity of seizures, and another patient still presented convulsions but followed the diet poorly [20]. In this paper, Talbot et al. also mentioned some effects on alertness, nervousness, and excitability (Table 1) [20]. Talbot also published a review in 1928 on different studies showing the efficiency of KD for epilepsy [21]. Helmholz reported the impact of KD on 144 patients with epilepsy and the reasons of treatment failures [22]. The diet was hard to follow, and there were constant breaks in the diet. The KD freed 31% (46/144) of the patients from seizures and improved an additional 23% (34/144) of patients. Finally, McQuarrie & Keith published an article suggesting the direct relationship between the degree of ketosis and the effectiveness of the KD in preventing epileptic seizures, reminding that the diet must be adjusted for each person to meet his particular requirements [23]. Their statements are illustrated with two children with epilepsy.

4. Discussion

The 1920s marked the beginning of the use of the KD for patients with epilepsy. By studying the literature on the history of the KDT, we realized that it was not clear if Wilder published one or two papers in 1921 to introduce the KD. There are indeed two Wilder papers that exist, published consecutively on July 27 and on July 28 in *The Clinic Bulletin* in 1921, which constitute the origins of the KD.

Wilder first formulated his hypothesis that the benefits of fasting on seizures might be dependent on ketonemia and that possibly equally good results could be obtained with a KD, very rich in fat and very low in carbohydrate, which would provoke ketogenesis [9]. Secondly, in his following paper, he studied for the first time the effects of a KD on 3 patients with epilepsy [10].

Wilder's hypothesis was based on the observation of the results obtained with fasting at the Presbyterian Hospital, New York, by Dr. H. R. Geyelin [14]. Geyelin subjected 26 patients with epilepsy to periods of absolute fasting, and a good proportion of patients remained free from seizures during the fasting and several months after the fasting. Geyelin himself first observed three patients with epilepsy treated by the osteopath Dr. Conklin who applied a fasting period of 15 days, followed by a feeding period of three weeks duration, and then by a second fast of 4–5 days, before applying fasting to one patient with epilepsy, and then to 26 patients with epilepsy. In the first patient of Dr. Conklin, after the second day of fasting, the seizures ceased; the second patient remained entirely cured for two years, and the third patient was seizure-free for three years. Conklin published an article on the use of fasting to treat epilepsy only in 1922, one year after the publication of Geyelin's paper [24] (Fig. 3).

Quickly following Wilder papers, several studies of the effects of KD on patients with epilepsy took place. We found a total of 9 papers on KD published in the 1920s with approximately 421 patients with epilepsy studied. The number of papers described in this article might not be exhaustive. It is worth noting that the way to conduct the classic KD is the same since the description of Peterman [16]. He reported the importance of dietary compliance. He also noted that hyperketosis could be efficiently managed by administrating carbohydrates by providing orange juice [17]. As there was no effective antiseizure treatment for patients with epilepsy in the 1920s, this probably explains why the KD was widely used in a large number of patients. However, with the appearance of the first antiepileptic drugs (e.g., the discovery of diphenylhydantoin by Merritt and Putnam in 1938), KDT use declined. Their use expanded again in the late 20th century, and there are now evidence-based studies including randomized trials [1]. Interestingly, an effect of the KDT on the comorbidities has been already mentioned in the early use of the diet [17,20]. This remains a subject of investigation with a need of stronger evidence [25].

Wilder elaborated his hypothesis believing that the benefits of fasting on seizures might be dependent on ketonemia and that a KD would provoke ketogenesis. Ketosis seems rather a marker of the

KD than its unique mechanism. Most of the studies on ketosis have shown an absence of correlation between blood ketone body concentrations and seizure frequency changes [26]. In experimental studies, seizure tests (6 Hz test, kainic acid, maximal electroshock, or pentylenetetrazol) distinguish intermittent fasting from the KD [27]. Moreover, nonketotic diet changes could also provide anticonvulsant properties [28]. Years of experimental studies suggest that the KD is probably effective through multiple mechanisms [29].

One century after the hypothesis [9] and the first report of Wilder's clinical experience [10], KD is an evidence-based treatment. Early in the history of the KD, Weeks et al. conducted an experimental approach to evaluate various forms of dietary treatments [15]. We are now talking about KDT because multiple dietary treatments such as the modified Atkins diet and the low glycemic index diet are effective for patients with pharmacoresistant epilepsy. The current history is marked by new indications of KDT for neurological diseases that are emerging such as brain tumor. The effects of KDT beyond seizures (cognition, comorbidities, and Quality of life (QoL) are a hot topic waiting for more evidence-based data.

Declaration of competing interest

The authors report no conflicts of interest.

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