

Denis Parsons Burkitt (1911–1993)

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At the beginning of our careers, each of us has the dream of someday making a discovery that will change the way our respective disciplines regard something we now regard as fact. Denis Parsons Burkitt was able to change the course of our thinking twice in his career. More remarkably, the two discoveries were, to the casual observer, in widely different fields of study, i.e., the elucidation of the origin of a tumor common in children in parts of Africa and the observation that dietary fiber deficiency is related to many of the chronic diseases of the Western world.

Denis Burkitt was born in Enniskillen, Northern Ireland, on February 28, 1911 and received his Bachelor of Medicine degree from Trinity College, studied surgery in Edinburgh, and later received his medical degree from Dublin University. His father, a

surveyor in County Fermanagh, was an ornithologist and was credited as the first to use banding of birds to study their territories, an interest in geographical distribution later shared by his son.

After serving in Africa and Sri Lanka as a surgeon during World War II, Burkitt joined His Majesty's Colonial Service in Africa. It was at Mulago Hospital, Kampala, Uganda, in the late 1950s that Burkitt was introduced to a facial tumor usually observed in young children. The severity of the tumors and the inadequacy of available treatments led him to further examine the incidence and distribution of this tumor. Beginning with a grant of £25, he surveyed hospitals across Africa by mail, putting together a distribution map that suggested, for the first time, an ecological effect on distribution of a cancer. Results of these early observations of the tumor and of the survey were published in 1958 (Burkitt) and 1961 (Burkitt and O'Connor), respectively.

During a trip to England in early 1961 to report his early results on this tumor, Burkitt met Tony Epstein of the Bland Sutton Institute at a seminar presented at Middlesex Hospital. Although Epstein had attended Burkitt's seminar almost by chance, he soon realized that the tumor described by Burkitt might be viral in origin, supporting his hypothesis of cancers induced by viruses. At that time Epstein and others had observed viral induction of tumors in experimental animals and had suggested a viral origin for some human tumors. Epstein and Burkitt met, and Burkitt agreed to ship biopsies from tumors to Epstein for further study. This arrangement led to the discovery of electron microscopic evidence of a virus in the tumor cells and eventually to the discovery of the Epstein-Barr virus, which has since become implicated in a wide variety of disease states. Several years later, when Epstein and Achong published a compilation of work dealing with the Epstein-Barr virus, Epstein gave credit to his attendance at this seminar as a turning point in its discovery.

Later in 1961, Burkitt and two colleagues departed on a trip that would take them more than 10,000 miles by car to examine the precise limits of the occurrence of the tumor in western Africa. This

monumental task was undertaken with a grant of £400 from several sources, including the British Medical Research Council (MRC), and was completed for £678. Initially, altitude and temperature were thought to be the determining factors, but further examination suggested rainfall as equally important. This suggested to Burkitt and his colleagues that the tumor might be spread by an insect vector. Subsequent identification of the virus and study of the lymphoma led to elimination of insects as a direct vector but demonstrated that the virus was expressed as a result of the depressed immune system of children with malaria. It was at a conference sponsored by the International Union Against Cancer early in 1963 that the tumor first became commonly known as Burkitt's tumor, a name that was later modified to Burkitt's lymphoma as a result of a more thorough understanding of its nature.

Early in 1964, Burkitt resigned his post with Mulago Hospital to assume a position with the MRC and make way for African surgeons in the newly independent Uganda. His new post allowed him to continue his work with lymphoma patients and teaching at the Makerere Medical School. He remained concerned for treatment of the lymphoma because surgery only prolonged the patient's life. The lack of X-ray treatment facilities in Africa led to examination of a series of chemotherapeutic agents. In usual fashion, Burkitt was able to secure a supply of drugs for his experiments by suggesting to the drug companies that his patients offered the chance for a controlled experiment because none had been treated with X-rays. The success of chemotherapy (methotrexate, cyclophosphamide and others) was amazing, with much lower doses being needed than had been reported for these agents for other tumor types.

In 1966 Burkitt returned to England and continued his work with the MRC and, during the following year, met naval Surgeon Captain T. L. Cleave, who described his hypothesis concerning refined carbohydrate as the cause of many of the chronic diseases of the Western world. Burkitt saw in Cleave's work a similarity to his early observations of the lymphoma, i.e., that several seemingly unrelated diseases might have a common cause. His own observations of the absence of these diseases in Africa and his increasing awareness of their prevalence in Western populations heightened his interest in this hypothesis.

Burkitt's foray into the fiber field again entailed two of his principal traits: a sharp, analytical mind and unflagging energy. In the preface of Burkitt and Trowell's book *Refined Carbohydrate Foods and Disease: Some Implications of Dietary Fibre* (1975) they state, "Our combined experience suggested that relatively imprecise information can be of epidemiological value." The book was dedicated to Surgeon Captain Cleave.

In the first two chapters of the book Burkitt delineates the philosophy that led him in his quest for answers, namely, that one must determine the geographical distribution of a disease in certain communities or in particular groups within that community that manifest a certain disease and then seek the environmental factors that are prevalent in areas or groups exhibiting a high frequency of that disease and absent where the disease is rare. His observations (usually illustrated with simplistic cartoons that made telling points) led him to derive associations between groups of disease conditions that were associated with Western civilization. From Burkitt's work and that of Trowell, there emerged the fiber hypothesis, which suggests that diets low in fiber may underlie development of many characteristically Western diseases.

Two papers published early in Burkitt's pursuit of the role of fiber in diseases of the developed world (Burkitt 1969 and 1971) outlined many of the epidemiological relationships among gastrointestinal diseases in various countries. He observed that similar diseases with similar incidence in similar populations might have similar causes. The causal factor that he selected to examine in the populations he studied was dietary fiber.

Later Burkitt (1979) wrote a short, popular book that reflected his simple yet forceful writing style and delineated his nutritional philosophy more thoroughly. The book was called "*Don't Forget Fibre in Your Diet*" and the subtitle added "to help avoid many of our commonest diseases." This book simplified the views on fibers and colon cancer that appeared in his 1975 book with Trowell.

Burkitt hypothesized that the increase in bowel cancer incidence observed in Western countries was due to changes in food, meaning reduction in the amount of cereal fiber and increases in protein, fat, refined starchy food and sugar. He also suggested that fecal bacteria might play an important role in the causation of bowel cancer. The average incidence of colorectal cancer in the United States, England and Scotland was, at the time he wrote this book, four times that in Japan, South India and Uganda. The level of *Bacteroides* in the feces was similar for all six countries, but the three locations with lower cancer incidence had significantly more *Streptococci*. Thus the ratio of *Bacteroides* to *Streptococci* in the United States, England and Scotland was significantly higher than the ratio in the other three locations. The ratio of fecal neutral to acidic steroids was much higher in the three countries with low colon cancer incidence, and both neutral and acidic steroids were degraded to a lesser extent in countries with a low incidence. Burkitt postulated that the amount of carcinogen formed would depend on variety and number of fecal bacteria, on the metabolism of bile acids in the gut, and on the time available for their bacterial degradation. Retention of carcinogen in the large bowel

would depend on transit time, frequency of defecation and inhibition against immediate evacuation when desire is felt. How many publications in the bowel cancer field owe their origin to these views?

During this same period of time, Burkitt, with Alec Walker and Neil Painter, contributed a similar review to the *Journal of the American Medical Association* (1974). In it they described the dietary fiber hypothesis in a way that undoubtedly launched the fiber era in the United States. This paper cited several observations by the authors that indicated a much lower incidence in Africa of several diseases that were prevalent in the United States. Included in the list were heart disease, appendicitis, diverticular disease, gallstones, varicose veins, hiatus hernia, hemorrhoids, colon cancer and obesity.

Several hypotheses, based largely on epidemiological evidence, concerning the potential role of dietary fiber deficiency in the causation of these disorders were presented. A strong case was made for a link between appendicitis and several other gastrointestinal diseases (diverticular disease, ulcerative colitis and colon cancer), with appendicitis being a predictor of the development of the other problems within a population. All were related in that a low fiber diet resulted in increased transit time, reduced fecal bulk, and drier, less fluid intestinal contents, which would increase intraluminal pressures, increase time of exposure of contents (and potential toxins) to intestinal mucosa, and cause other similar changes. Subsequent research has substantiated some of these hypotheses, but their simplicity made the message of the relationship of dietary fiber to disease easily understandable by everyone and created an atmosphere that resulted in sustainable interest in this area of research, allowing investigation of these mechanisms.

Burkitt did not expound at great length on fiber and heart disease, leaving that to his colleague Hugh Trowell. He did comment, however, on high fat diets, high salt intakes, diabetes and obesity as risk factors for heart disease and suggested that exercise and diets high in cereal fiber might be protective. The hypothesis of Trowell and of Burkitt, Walker and Painter—that lower concentrations of plasma cholesterol and reduced incidence of heart disease occurred in populations that consumed high levels of dietary fiber—was summarized in the *Journal* review. They further suggested that these effects resulted from negative sterol balance as a result of increased excretion of bile acids, a hypothesis that has been shown to be true for some sources of dietary fiber. As with gastrointestinal function, this hypothesis has been found to be much too simple to explain the complex relationship between dietary fiber and heart disease. However, its simplicity made it understandable to a wide audience and gained support for the research that was and still is needed to define these relationships more thoroughly.

The use of epidemiological methods to develop wide-ranging hypotheses concerning, in this case, dietary fiber and disease was the essence of Denis Burkitt. If we examine the literature for evidence of the impact of Burkitt in the area of dietary fiber we find a predominance of papers commenting on the importance of dietary fiber in disease prevention or suggesting mechanisms by which this effect may be occurring. In the foreword to Burkitt and Trowell's book (1975) Sir Richard Doll wrote, "Once every 10 years or so a new idea emerges about the cause of disease that captures the imagination and, for a time, seems to provide a key to the understanding of many of those diseases whose aetiology was previously unknown... To these we may now add a deficiency of dietary fiber. But whether it will be as seminal an idea as that of vitamin deficiency or as sterile as that of stress, we shall probably not know for another 10 years."

Almost two decades have passed since those words were written. The dietary fiber idea has not faded. It has been refined and redefined, but the basic observations of Denis Burkitt still drive the research. We know much about fiber analysis, fiber structure and mechanisms of fiber action under specific physiological conditions. We now recognize the presence of other beneficial substances (carotenoids, phytosterols, etc.) in a high fiber diet. The discovery of these substances owes something to interest in the fiber hypothesis.

In addition to his cartoons, Burkitt was well known for his numerous slides of human feces taken on his early morning walks in the bush in Africa. He was often quoted as saying that the health of a country's people could be determined by the size of their stools and whether they floated or sank (complete with a cartoon), not by their technology. On one occasion he shocked even the gastroenterologists in the audience by asking, "How many of you men have any idea of the size of your wives' stools?" Although this discussion often led to laughter and to some interesting responses in the news media, none of us will forget the message it was intended to deliver, i.e., that increased fiber intake would increase stool weight and reduce stool density, two variables that were epidemiologically linked with a reduction in the incidence of several diseases.

Since 1975 the fiber literature has increased exponentially. But this mass of literature originated in the few lucid papers written on the basis of observation rather than sophisticated research. The state-of-the-art equipment helps us to learn more about the fiber phenomenon, but we must never lose sight of the fact that the origin of this knowledge was a result of cerebration not instrumentation.

Denis Burkitt received many awards during his career, being named an honorary fellow of Trinity College, a Fellow of the Royal Society and a member of the French Academie de Sciences, and receiving numerous honorary degrees and, in January 1993, the Bower Award and Prize in Science. In spite of these

honors Burkitt remained humble and modest, suggesting that in science, as in life, "...attitudes are more important than abilities, motives... than methods, character... than cleverness, perseverance... than power, and the heart always takes precedence over the head."

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