Denis Burkitt: A legacy of Global Health

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ABSTRACT: When first described in 1958 (1), Burkitt lymphoma (BL) was considered by many to be an African curiosity. Descriptions of a unique clinical cancer syndrome (2) and the geographic distribution (3) of the lymphoma aroused much greater interest and, over the next few decades, over 10,000 publications on BL would influence many facets of oncology research including immunology, molecular genetics, chemotherapy, and viral oncology (4,5). Rare in developed countries, it represents 30-50% of all cancers in equatorial African children (6). At the time of discovery its distribution along equatorial Africa was unique; it was where a child was born and lived, and not what race they were, that conveyed the greatest incidence risk (2,3). Its association with Ebstein-Barr virus (EBV) brought attention to the possibility that oncogenesis may be influenced by viruses (7,8). It is also tied to malaria, with higher incidence in regions of greater malaria transmission (6,9). It was one of the first cancers to be cured by chemotherapy alone (10), which likely provided much needed encouragement to early chemotherapists. The influence that BL had on furthering oncology is far-reaching, and it is fitting that the physician credited with bringing attention to this disease was himself broad in his influence. Denis Burkitt was a humanitarian surgeon whose work was not limited to Burkitt lymphoma: he instigated a plan to rid an entire Ugandan district of yaws, he designed and created affordable orthopaedic equipment that could be locally produced in Kampala, and he was an early advocate of a high fiber diet (11,12,13). His story is presented here, with a focus on how one determined surgeon was able to contribute so much to the advancement of surgical global health.

Denis Parsons Burkitt was born in Lawnakilla, County Fermanagh, in Northern Ireland in 1911. His family was deeply religious, and his own religious convictions would guide his humanitarian service as a physician (13). His future as a doctor was almost finished before it had even begun when, at the age of 11, he lost his right eye following a stone throwing fight between two gangs of boys (7,12). At the age of 18, Denis entered Trinity College in Dublin to study engineering. He would transfer into medicine before finishing his first year, convinced that his calling was to become a physician. Finishing second in his final qualifying exams of medical school, Denis would go on to appointments in Scotland and England. In 1938, Burkitt would pass the Fellowship of the Royal College of Surgeons of Edinburgh (7). Recently graduated, he signed up for a 5 month voyage to Manchuria as a ship's surgeon on a Blue Funnel Line freighter. During this prolonged voyage at sea, with time to think about his future, he became convinced that his future lay as a surgeon working in the developing world (7,12).

Returning to England he worked as a resident surgical officer in Plymouth. However, he did not lose sight of his goal of working in Africa. In 1940 he applied to join the Royal Army Medical Corps (RAMC), but was not accepted. In 1941 he applied for service with the Colonial Office in West Africa, and was once again rejected. Even still he was not deterred. Later that same year he applied again for service with the RAMC and was accepted (7). His first deployment took him to Kenya and Somalia, and then to Ceylon and Singapore. During his time with the RAMC he was able to visit Uganda for six weeks (12). Back in England after the war he turned his focus to Uganda, having decided that this was the country where he was called to work, and applied again to the Colonial Office in 1946.

Lango District and Early Work in Uganda

This time his application was successful and the young surgeon was given a post as the district medical officer in the 100 bed hospital in the town of Lira, the capital of Lango district in Northern Uganda, with responsibility for the medical needs of 250 000 Ugandans (11,12). Driven and hardworking, Burkitt would perform more than 600 operations in his first year in Lira alone, while previous medical officers had done no more than ten major operations a year (11). It was not only with his scalpel that Burkitt worked: noticing that about 80 percent of the population of Lango district was affected by Yaws, an infectious ulcerating disease cause by *Treponema* spirochetes, Burkitt formed a plan to eradicate this disease from his district. He requested funds to give every man, woman, and child in the Lango district a single dose of intramuscular penicillin to either prevent or cure the disease. Burkitt would be called away to work in Kampala before seeing his plan completed, but he would hear later about its resounding success – yaws had all but disappeared in the Lango district (11). Burkitt showed an interest in epidemiology immediately. He noted in a publication of 200 cases of primary hydrocele that in eastern Lango district 30% of males were affected while only 1% of their counterparts in western Lango district were stricken by this disease (14). The explanation for this observation was later shown to be due to the distribution of filariasis (7).

In 1948 Burkitt was transferred to the Mulago hospital in Kampala to take over for Dr. Ian McAdam who was sick with a peptic ulcer (11). After moving to Kampala he became an Honorary Teacher in Clinical Surgery at Makerere University College Medical School, which, at the time, was the only college training African physicians from Uganda, Tanzania, Zanzibar, and Kenya (11). Burkitt made an immediate impact in Kampala contributing to the care of orthopaedic patients stricken with poliomyelitis and tropical leg ulcers. Frustrated with the number of patients with crippling diseases who needed amputations, Burkitt used his first precious home leave back to England in 1949 to take a five months orthopaedics course in London (11). Fortified with new orthopaedic knowledge and perhaps drawing on his brief engineering training, Burkitt organized the production of callipers and crutches from low cost, local materials (12). He also fashioned

artificial legs himself using malleable plastic, pole, and tire rubber, which could be made for about $4.00 (11).

Burkitt Lymphoma

Burkitt would spend 9 years in Kampala before encountering the patients who would be catalysts for the discovery of the tumour that bears his name. In 1957 he saw a 5 year old boy with a tumour of the jaw. Visiting Jinja Hospital a month later, Burkitt saw a girl with a similar tumours in her jaw as well as tumours in her abdomen. Both patients died, and Burkitt searched the Mulago hospital records finding similar past cases of jaw and abdominal tumours (12). The next year Burkitt described the tumour, which, without histological diagnosis, he incorrectly labelled as a sarcoma, in a scientific forum (1). At the time his paper aroused little interest (12,15). In 1961, Burkitt and a pathologist colleague, Dr. Greg O'Conor, published again, this time confirming the tumour as a lymphoma and describing the clinical syndrome of extremely rapidly growing tumours occurring in the jaw, abdomen, and, more rarely, in the salivary gland, bone, or spinal column (2). That same year O'Conor published on the histological aspects of BL, and noted the surprising absence of leukemia in patients with what was then called malignant lymphoma syndrome. O'Conor realized that a viral disease in cows, lymphocytic bovine leukemia, was similarly often subleukemic with a similar organ distribution as BL and advocated for consideration of a viral cause for BL (16). He also considered the "possibility of a priming action on the reticuloendothelium by some parasite with subsequent malignant change", a concept which is similar to today's understanding of B-cell hyperplasia being an essential component of pathogenesis for BL (6).

The 1961 publications garnered much more interest than the first, and an interest in the African jaw tumour grew. Burkitt had not discovered a new disease; he notes several earlier published case reports of jaw tumours in African children. However, Burkitt brought new attention to the disease, and also worked to determine its distribution in Africa. In an old Ford station wagon Burkitt and two colleagues travelled from Uganda to East Africa to Johannesburg and back, stopping at hospitals along the way to interview medical staff and scour records for signs of malignant lymphoma (12,15). In the nearly 10 000 mile journey he was able to show that the frequency of the lymphoma was distributed across central Africa in a "lymphoma belt", and postulated that the etiology must be related to external environmental local factors (2). Later, he reported the lymphoma as being rare in regions of Africa with a minimum temperature below 60° F in the coldest season of the year, in regions with low rainfall, and in regions with altitudes above 5000 feet (3). That the tumour was commonly found in hot, moist, tropical regions raised the possibility of an insect-vectored virus (9). Soon after, others were writing about the possible link between malaria and BL (17), and considering the possibility of the anopheles mosquito as a vector (18). In 1964, the discovery of a virus (eventually named the Epstein-Barr virus) seen in lymphoblasts isolated from a BL patient (19) would again push research onwards. The discovery of EBV as the first human cancer virus (6,8), would pave the way for investigations into the cancer causing potential of human herpes virus type 8, human papilloma virus, hepatitis C virus, and others. With current estimates of 16% of all cancers being attributed to viruses worldwide (20), the importance of the discovery of Epstein-Barr virus as a precedent cannot be overstated.

Over the following decades major steps were made in understanding the pathogenesis of BL. The disease was divided into "endemic BL" which occurred in high incidence regions in Africa and Papua New Guinea and "sporadic BL" which occurred in low incidence regions (21). In 1982 a case series of four homosexual men with BL was published (22), prompting further research and the eventual inclusion in the WHO classification of haematological malignancies of immunodeficiency-related BL (21). Further studies investigated the genetic events instigating the disease. We now know that oncogenesis in BL is universally related to specific chromosomal translocations leading to deregulation of the *C-MYC* oncogene. Abnormalities in *P53* and *ARF* pathways also play a role (6,23). Unfortunately, civil disturbances in Africa have disrupted ongoing research and many questions are left unanswered. Efforts to determine if preventing EBV and malaria would prevent BL were abandoned (5). Efforts to provide treatment for BL and other cancers in Africa have also been affected by civil and military disturbances, and African children with BL continue to lack access to adequate medical care (5,23,24).

A Search for the Cure

Burkitt lymphoma was quickly fatal, with most children living only a few months following presentation. Radiotherapy was not available at the time in East Africa, and Burkitt writes about a case of a child who was flown to Bombay for radiotherapy who initially showed rapid regression only to die a few months after returning to Uganda with a relapse of his disease (2). Due to the systemic and multifocal nature of the disease radical surgery also proved hopeless (25). With nothing else to offer, Burkitt tried injecting nitrogen mustard into the external carotid artery of afflicted patients for palliation, which again led to rapid regression followed by relapse and death a few weeks later (2). Early efforts with cyclophosphamide, methotrexate, and vincristine were similar. In the early 1960s the majority of patients had long term survival rates of only 20%, despite treatment with chemotherapeutic agents (25). Burkitt and other researchers began to publish frequently about the management of the disease, and research focussing on advancing the chemotherapeutic treatment of Burkitt lymphoma would be spurred onwards by collaboration between the Uganda Cancer Institute and the United States National Cancer Institute starting in 1967 (25). In the 1970s treatment had evolved to incorporate both multiagent therapy and intrathecal chemotherapy, and new treatment strategies resulted in an increase in overall survival from 20% to 50% (25). Today high intensity short duration chemotherapy with CNS prophylaxis has greatly increased survivability in children with Burkitt lymphoma to a five year survival of 87%-93% overall in developed countries (26,27). Unfortunately the survivability in Africa has not improved as dramaticall. When Burkitt left Uganda in 1966 to work with the National Research Council in the U.K., he estimated that long term survival was achieved in 20% of cases with treatment (10,28). If Burkitt was alive today he would find that in the fifty years since he left Uganda the outcomes of African children with Burkitt Lymphoma has only improved marginally, with a reported cure rate that is usually less than 50% (29).

Cancer Treatment in Africa and Global Health

Burkitt lymphoma continues to be a significant cause of morbidity and mortality for children in equatorial Africa. Though the disease is considered treatable in developed nations, the majority of children who develop BL in Africa lack access to adequate care

and face significant socioeconomic challenges that limit their care (5,23,24). Delay in presentation and diagnosis also contribute to higher mortalities (30). The outcomes of BL patients in Africa remain dismal, as do outcomes of most cancer patients in Africa (5,29,31). Children undergoing BL treatment in Africa are more likely to die from complications of treatment (e.g. infection, tumor lysis syndrome) than from relapse of the disease itself (24), which is a testament to the difficulties of delivering optimal care in low resource centres. It is likely that a complex mix of medical, socioeconomic, cultural, and environmental factors contributes to poor outcomes. To tackle these factors, the Institute of Medicine, an NGO that aims to provide independent and objective information to policy makers (32), has called for the global health community to collaborate to promote cancer awareness and advocacy, to provide appropriate aid for cancer-control projects, and to focus on cancer control and prevention (30).

Cancer in low and middle income countries is minimally represented in global health efforts (30,33). In 2010 fewer children in Africa received life-saving chemotherapy for BL than they did in the 1960s and 1970s (31). In the past a global trend towards reduction in the health inequality between low, middle, and high income countries existed. However, since the early 1990s the trend has reversed, and health inequality is now increasing (34). Similarly, the difference in life expectancy, measured using the population-weighted dispersion measure of mortality (DMM), was converging between 1950 until the late 1980s, but from the 1980s to the year 2000 the trend shifted to a widening of disparity between low and high income countries (35).

The legacy of Denis Burkitt is testament to the critical role surgeons play in cancer diagnosis and treatment in resource poor settings. Burkitt spent nearly 20 years living and working in Uganda, and during this time contributed enormously to the health and wellbeing of his patients. Though there are success stories, the disparity that still exists - and seems to be growing - between low income and high income countries should spur the international medical community to take up the task set upon by Burkitt and his colleagues – to work towards a future where life expectancy is not determined by which country one lives in.

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