

# Burkitt's Lymphoma: The Discovery and Diagnosis of a New Illness

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## **Abstract**

How medical practitioners make a diagnosis is not well understood. When confronted with what is apparently a new disease, the diagnostician faces a special, perhaps revealing, challenge. In this paper I use the special circumstance of African Burkitt's lymphoma as an apparently new disease to examine how it was recognized, characterized, and diagnosed between 1958-1963. African Burkitt's lymphoma seemed strikingly new when it was first detected at a district hospital in Uganda. It puzzled Denis Burkitt and the pathologists who worked with him for about five years. After much study and time, they could only agree that it was a malignant tumour, likely some type of lymphoma. Eventually, the particular geographic restriction of its occurrence and its distinctive distribution in the human body were the features that led to its recognition as a specific entity able to be diagnosed. The controversy that unfolded over five years shows how clinicians proceed to diagnosis, particularly when confronted with what appears to be a new disease.

## **Résumé**

On ne comprend pas encore très bien la manière dont les médecins praticiens établissent un diagnostic. Lorsqu'il est confronté à ce qui semble être une nouvelle maladie, le diagnosticien fait face à un défi particulier, voire révélateur. Dans le présent article, l'auteur utilise la situation particulière de l'apparition du lymphome de Burkitt africain en tant que maladie apparemment nouvelle pour examiner comment il a été reconnu, caractérisé et diagnostiqué entre les années 1958 et 1963. Le lymphome de Burkitt africain semblait étonnamment nouveau lorsqu'il a été détecté pour la première fois dans un hôpital de district, en Ouganda. Il a intrigué Denis Burkitt et les pathologistes qui travaillaient avec lui pendant environ cinq ans. Après y avoir consacré beaucoup d'étude et de temps, ils n'ont pu que convenir du fait qu'il s'agissait d'une tumeur maligne, probablement une sorte de lymphome. Au bout du compte, la restriction géographique particulière de son apparition et sa répartition particulière dans le corps humain ont été les caractéristiques ayant mené à sa reconnaissance en tant qu'entité spécifique, pouvant faire l'objet d'un diagnostic. La controverse qui a duré cinq ans montre comment les cliniciens en arrivent à un diagnostic, particulièrement lorsqu'ils sont confrontés à ce qui semble être une nouvelle maladie.

*Keywords: Burkitt's lymphoma, discovery, diagnosis*

## Introduction

Diagnostic work is essential to medical practice because it is a little-acknowledged fact that the truth about the patient's particular illness is not usually known for certain – often, even after death with that illness, at autopsy. Moreover, diagnostic activity determines which illness a particular patient likely has at a particular time. Thus expert clinicians are always examining, updating, and re-confirming or refuting any earlier diagnosis.

Diagnosis normally proceeds when the patient's presentation profile – symptoms, signs, and laboratory test results – is typical and familiar. Things get complex when it is neither. Several considerations engage the clinician's mind when additional cognitive and investigative work yields no progress. The patient may have no somatic abnormality recognizable as an illness (disease, defect, or injury) but may be suffering from the effects of the stresses of life and manifesting it as bodily suffering. Sadly, this juncture often results in inappropriate dismissal of the patient and frustration for both clinician and sufferer. A better strategy unfolds when the clinician is convinced enough to acknowledge that something indeed has gone wrong with the patient's body, but it remains obscure. At this point, consultation is in order. A more interesting diagnostic process occurs more rarely and in special circumstances. The first-contact physician and consultants, agree that the patient has a specific illness, but no one knows what it is. Usually it turns out to be simply an unusual presentation of a rather usual disease, but occasionally it turns out to be genuinely new to the medical mind. Legionnaire's disease, HIV-AIDS, and SARS COV-2 disease are recent examples.

A study of the recognition of a new disease may shed light on our understanding of diagnosis: how the disease was recognized, how was it determined to be new, how it was characterized and defined, and how it was accepted as a new disease. I believe enough time has elapsed, and sufficient information has accumulated to permit the use of African Burkitt's lymphoma to stand as a case in point. In this paper, I use this example to consider how Burkitt realized he was confronted with a new disease and went about getting the necessary information and help to be sure that it was so and then to determine its nature.

## First Appearance

New diseases rarely fall from the sky, but they sometimes seem to have done just that, as in SARS. More typically they

have antecedents, but they are not recognized as such until a prepared mind sees the disease for what it is. Burkitt's lymphoma was no shooting star, but Burkitt's first paper published in 1958 is generally accepted as the first recognition report.<sup>1</sup> Not until 1963 were the basic defining characteristics of the disease, and its place in the prevailing lymphoma classification, provisionally settled. Thus, in this paper, I will concentrate on these delimiting years.

Denis Parsons Burkitt (1911–1993), an Irish-trained surgeon, began his work in Africa in an upcountry hospital in Lira, Luongo District, Uganda (1946–1948). The hospital is situated in the midst of what was later found to be Burkitt's lymphoma territory.<sup>2</sup> However in recollections about his discovery, he states that he saw nothing like it during his time there.<sup>3,4</sup> He subsequently moved to Mulago National Referral Hospital in Kampala where he worked for most of the next two decades. Of special note, an American pathologist, JNP Davies, also began working there in 1950. Davies was interested in the unusual cancers in Africa and their possible causes. As we shall see, he had already begun a cancer registry, and his work and skill proved to have an important role in Burkitt's discovery.

From Burkitt's initial paper in 1958, "A sarcoma involving the jaws in African children,"<sup>1</sup> his thinking was already quite advanced. The presentation of the tumour in these children was abnormal, unusual, distinctive, and prevalent:

"A sarcoma involving the jaws in African children has recently come to be recognized at Mulago Hospital as a distinctive clinical condition and certainly the commonest malignancy of childhood."<sup>1</sup>

While Burkitt may have had a prepared mind, he was also favored by numbers because he had 38 likely cases to report in his first paper. He stresses that jaw presentation is the commonest, affecting one to four jaw quadrants. Also, 15 of his 38 cases had tumour deposits in other organs: adrenal glands, thyroid, testes, kidneys, liver, stomach, pancreas, salivary glands, cranium, and femur. Of note superficial lymph nodes were rarely involved. Burkitt is clearly puzzled by this behavior of what he believed was a sarcoma: although the clinical presentation is distinctive, "its site of origin and nature remain obscure."<sup>1</sup> He looked to JNP Davies for some histopathological help. Burkitt quotes his pathology report directly in his first paper:

"The tumours are of a highly malignant type with very numerous and often atypical mitoses...These cells

occur singly or in clusters, often in rounded otherwise clear spaces..., strongly resembling lymphocytes; in some cases the tumour resembles a lymphosarcoma.... Small tumour giant cells are seen, in many cases resembling those seen in Hodgkin's disease..."<sup>1</sup>

Davies is evidently referring to the 1942 Mallory and Gall non-Hodgkin lymphoma classification here.<sup>5</sup> While the two particular cell types and the distinctive spaces between them strike Davies' eye, he refrains from offering a definitive diagnosis. Thus Burkitt remained puzzled, and he attempted to establish some sort of synthesis for all these facts:

"It is unlikely to be a primary jaw tumour with metastases. If the original tumour was a single primary it would require a mode of spread to other jaw quadrants which is not known to exist. This difficulty disappears if multiple tumours in the jaw are postulated. In either case, however, the pattern of metastases elsewhere, mainly to the contents of the abdomen, again involves a manner of spread quite unlike that of any known tumour. Furthermore, in one patient in this series the abdominal tumour preceded the appearance of the jaw tumour by at least 6 months. In another a tumour in the testis was observed first. This was followed by an abdominal tumour and loosening of the teeth. At autopsy both kidneys and adrenals were found grossly involved in tumor and deposits were demonstrated in the jaws.

"The primary growth might be abdominal, the tumour in the jaws metastatic.

"The other possibility is that multiple primaries appear independently in jaws or abdomen, or both. An abdominal sarcoma of similar histology, occurring in the same age-group but without involving the jaw, is not rare at Mulago Hospital."<sup>1</sup>

This attempt at an analysis did not advance his understanding. Nevertheless, Burkitt's diagnosis of sarcoma of the jaw seems to account for more facts than any other disease, albeit unsatisfactorily. He concludes:

"It may well be that in Uganda we have a syndrome of diverse characteristics and that this series of jaw sarcomata is no more than a group which has attracted attention owing to its very striking clinical features."<sup>1</sup>

However even as a jaw sarcoma, it remains "a syndrome which has not been previously fully recognized."<sup>1</sup> He might

have used the opportunity to stress that it is a distinctive disease, and while generally unusual, it was prevalent at his hospital. Burkitt remained committed to the idea that this was a localized disease if only he could determine where it began, the initial site, and how it subsequently spread.

This reluctance to dismiss the possibility that the disease process has a specific location is typical of the practitioner experienced in diagnosis because it is well appreciated that diagnosis is much easier when it is known that the disease has a specific location. Once convinced that something is abnormal, clinicians typically think first about which body region could be involved. Thereafter consideration for disease of an organ, tissue or cell type can proceed. While Burkitt could not be certain the disease was indeed localised, he did have something that not every diagnostician confronted with the possibility of a novel illness has: the secure knowledge that the general nature of this one was specifically that of a malignant tumour.

## Expert Appraisal

Perhaps it is a happy coincidence that Davies, the pathologist, had published his second report from the Kampala tumour registry in August of 1958,<sup>6</sup> while Burkitt's first paper appeared in November of the same year. Davies had a clear idea in mind for creating the tumour registry:

"The incidence of cancer amongst the indigenous inhabitants of the African continent has not been established in any area, ... if differences could be clearly demonstrated they might throw light on possible environmental causes of cancer..."<sup>6</sup>

Among the results in his report is a greater than expected number of tumours of the lymphatic system. However, because the survey is beset by sampling difficulties, the significance of this observation is uncertain. In 1960 Davies published his first paper on Burkitt's tumour, this time with a radiologist, his brother, AGM Davies.<sup>7</sup> While the authors grant that Burkitt "who first recognized the remarkable frequency of these tumours in African children," they state that the jaw tumours are also the commonest ones seen by a radiologist and that the numbers are "quite astounding."<sup>7</sup> (Burkitt had already noted in his 1958 paper that the bone tumours were radiologically osteolytic and often evident before the symptomatic tumour manifested.) Also, careful scrutiny at autopsy revealed tumour deposits in the

retroperitoneum and abdominal lymph nodes in addition to the sites mentioned by Burkitt. The authors then engaged in another search for a pattern as a preliminary to diagnosis:

“This tumour presents as a clear cut clinical entity which, now we are aware of it in Uganda, can be recognised at sight... We have given considerable thought to the status of this tumour. Metastatic malignancy of the jaws is infrequent... and if this was a metastatic tumour we should still be left with the problem of the primary tumour and the reasons why it should so frequently and so selectively metastasize to the jaws, and not to other bones. The only channel of metastasis would be by the blood stream.”<sup>7</sup>

They continue by considering neuroblastoma, which is also frequent in their experience, but the histology is incompatible. Ewing sarcoma is mentioned but is dismissed for its distinctive histology and the fact that jaw bone involvement is rare. For similar reasons, reticulum cell sarcoma of bone, multiple myeloma, plasmacytoma, and lymphoepithelioma are also dismissed as possibilities. While it is clear that Burkitt has demonstrated to their satisfaction that a transparent cut clinical entity exists and their pathology shows that it is a malignancy, the specific nature of the disease process remains unknown. They decide to label the tumour as a “multicentric sarcoma.” They remain unconvinced as to whether it is new. They say that if a new disease is present then “it seems possible that we are dealing with a local carcinogenic influence with a remarkably selective and local potency.”<sup>7</sup>

A few months later, with the help of a pathology colleague, JNP Davies published a further report on the pathology.<sup>8</sup> They were convinced that the clinical and histological appearance of the jaw and the non-jaw tumours is identical. Furthermore, they would now include many of their former and frequent neuroblastoma cases in the group described by Burkitt, which “should be classified as lymphomas.” An updated account is given of the histopathology as “poorly differentiated lymphocytic lymphoma or lymphosarcoma.” The clear spaces or “water pot” effect is seen “almost as a trademark” in these tumours. The histopathology has allowed a conviction that the tumour is the same regardless of where it first appears, which obligates the abandonment of the localized disease presumption. This switch in commitment to a multicentric origin led them to consider the tumour a lymphoma rather than a sarcoma. However, the authors limit their change in perspective to the pathology

description. They do comment on novelty but on non-pathological grounds:

“The outstanding incidents of localization in the jaw in our cases is indeed unique and would seem to be a real geographic or epidemiologic phenomenon.”<sup>8</sup>

The next important publication was actually a two-part paper in 1961.<sup>9,10</sup> The general term “malignant lymphoma” is introduced to mean “the general category of tumours of the reticuloendothelial or lymphoreticular system... of lymph node or of extranodal origin.”<sup>9</sup> After adding an additional potential site of tumour occurrence, the CNS, Burkitt lists the distinctive features of the syndrome: an extremely high incidence; an apparently limited geographic distribution; a striking and specific age distribution; and a characteristic and unusual anatomical distribution, particularly in the jaw. He calls it “a clinical syndrome.”<sup>9</sup> In the companion paper published with the pathologist O’Connor, they openly call the tumor a “pathological entity.”<sup>10</sup> One can quarrel with the use of the term “syndrome” here, but it reflects the author’s desire to retain the perception that they do not have a distinct pathologic basis for it but rather a striking association of unusual occurrence features. In the pathology paper O’Connor comments that the gross pathology is not “significantly dissimilar in many respects to malignant lymphoma,” but that sheer force of numbers and “certain unique features” prompt him to classify and comment upon the histopathology. Despite the “surprising cytological uniformity” O’Connor distinguishes four cell types: stem-cell, histiocytic, lymphocytic poorly differentiated, mixed cell. He believes they arise from the primitive mesenchymal cell of the reticuloendothelial system. He speculates that the histiocytes may represent a host response rather than neoplastic cells. He attributes the clear spaces, called the “starry sky” or “water pot” appearance to lymphoproliferative activity. He states that the tumour is a pathological entity because of the cell types’ close morphologic relationship, which suggests a common cytogenetic origin.<sup>10</sup> Of interest, he also speculates that the tumour’s geographic distribution is similar to that of holoendemic and intense parasitemia from falciparum malaria, which was highly prevalent in young African children then. He wondered whether the capacity of the parasite to prime the reticuloendothelial system could lead to subsequent malignant change.<sup>10</sup>

A better definition of the pathology criteria was slow to emerge but the need to have them was great. As the striking geographical distribution became more evident, and with it

the need to understand the cause of the tumour, strict diagnostic criteria would be essential for outlining it. Late in 1962 *The Lancet* featured a lead article in an attempt to clarify matters for the wider medical community:

“The microscopic appearances do not differ essentially from those of lymphosarcoma elsewhere in the world...The peculiarities of this tumour in Africa are its monstrous frequency, the extraordinary nature of the jaw-bone lesions, and its geographical distribution.”<sup>11</sup>

An expanded group of pathologists in Uganda responded by a letter to the editor within 14 days:

“We feel that it is of great importance at this time to establish definite criteria for the diagnosis of Burkitt’s tumour...all cases should be biopsied, and...only those cases conforming to defined histological criteria should be included.”<sup>12</sup>

They go on to suggest that O’Conor’s classification was based on artefact. Their own study of the tumour with Giemsa and Leishman stains and histochemical techniques always shows “a poorly differentiated lymphoma.” On cytological study the histiocytes are non-malignant and the lymphoid cells “closely resemble” the lymphoblasts seen in acute lymphoblastic leukemia. Histochemically the lymphoid cells are similar to other lymphomas. They comment that the uniformity of the cells in the tumour do not justify the distinctions formerly made by O’Conor.<sup>10</sup> In the same Journal issue, Epstein and Herdson report that the electron microscopic structure of cells from two Burkitt lymphoma cases have a “similar fine structural organization to those of classical lymphomas.”<sup>13</sup> The debate carried on into 1964 with less emphasis being placed on the starry sky appearance and the cell uniformity and more on the nature of the lymphoblasts themselves.<sup>14,15</sup>

## A Search for an Answer

Because of the prevailing uncertainty over lymphoma classification in general and the absence of agreed diagnostic criteria based on its pathology, uncertainty persisted over whether Burkitt’s lymphoma was a new disease or a familiar one altered by a local environmental or geographic cause. Further, if it were to be considered as new, was it newly recognized or a *de novo* disease? The histopathology was

sufficiently advanced to allow a search for previously seen cases to answer that last question. In 1964 Davies published comments on the notes of Sir Albert Cook who was working at Mulago Hospital in 1901.<sup>16</sup> His report, and additional ones for 1905, 1910 and 1920, are now regarded as the first record of a disease resembling Burkitt’s lymphoma.<sup>17</sup> Many other reported cases across sub-Saharan Africa were retrospectively identified by Burkitt experts as likely cases: Nigeria 1934 and 1947, Cameroon 1953, Congo 1956, and Congo/Ruanda-Urundi 1957. They had been variously diagnosed as sarcomas or lymphosarcomas of the jaws or ovaries. So the answer to that last question is that it was most likely not a new disease as such but a newly-recognized one.<sup>18</sup>

Denis Burkitt appears to have been the originator of the idea that Burkitt’s lymphoma was geographically limited as he refers twice<sup>9,20</sup> to a conversation he had with South African cancer researcher A. G. Oettlé, in 1957:

“Shortly after the recognition of this clinical syndrome a discussion of the problem with Oettlé (1957, personal communication) revealed that the condition was unknown in South Africa. This suggested that the geographical distribution was limited, and an effort was made to determine the pattern of tumour occurrence.”<sup>19</sup>

This piece of negative information piqued Burkitt’s interest so he conducted a postal survey across Africa to ask about the tumour’s occurrence. He reported a belt-like distribution of Burkitt’s lymphoma across sub-Saharan Africa.<sup>21</sup> Work with a virologist at Entebbe indicated that the tumour distribution was congruent with an African geographic area delimited by a mean temperature above 60 degrees F, altitude below 5,000 feet and annual rainfall above 30 inches. He mused about the possibility of an arthropod-borne vector but is careful to note that JNP Davies had also suggested that this tumour might be virus-induced.<sup>22,23</sup> To confirm and get more detail on these limits Burkitt undertook a trip around southeast Africa, “a tumour safari” to enquire about this tumour occurrence. The results were congruent with what he already knew about its geographic distribution but yielded more detail for the east African countries.<sup>24</sup>

## Acceptance as a New Disease

By 1963 the Burkitt researchers had convinced the world that the lymphoma was a newly recognized disease, but on

non-pathology grounds.<sup>18</sup> The limited geographical occurrence was an essential part of the case definition. O'Connor, the pathologist, states unequivocally:

“Unlike many of the previous publications on this subject, I have not in this instance characterized the African disease by its geographical distribution...the two single features wherein the African disease differs from lymphosarcoma elsewhere show a definite geographic pattern and...both these features, the high incidence and the jaw predilection, apparently have the same geographic distribution.”<sup>25</sup>

Speaking as a pathologist then, O'Connor finds it unnecessary to postulate a new disease when the pathology was almost identical to that of a known disease.

In the year after this study's time of interest, Epstein and Barr created a cell culture of the lymphoma cells, finding that the sub-cellular microstructure was typical of lymphoblasts.<sup>26,27</sup> Later this same year they reported finding virus particles in the nucleus and the cytoplasm of Burkitt lymphoma cells that resemble herpes simplex in shape but were smaller in size.<sup>28</sup> Between the earlier speculation that intense parasitemia with falciparum malaria in young children had a priming role in the onset of lymphoreticular neoplasm, and this new and intriguing possible viral cause (now known as Epstein-Barr virus), the global medical community embarked on a decades-long consideration as to whether either or both were causal. Over the years the possibilities of genetic alteration, genetic selection or priming from one or both infectious agents have been joined in the continuing debate. While the unfolding result of this ongoing debate is beyond the scope of this paper, it is now accepted that Burkitt's lymphoma is a sporadically occurring form of B-cell, non-Hodgkin lymphoma. The disease is associated with Epstein-Barr virus and has a chromosomal translocation that activates an oncogene (*c-MYC*).<sup>29</sup> “African” or “endemic” Burkitt's lymphoma is the same lymphoma whose different occurrence and gross morphology are a result of factors particular to its setting in tropical Africa.

### Comment

What is interesting about the recognition of Burkitt's lymphoma is that it was based on its unusual geographic occurrence and its histopathology. That recognition took 5 years of collaboration between clinicians, radiologists, and

pathologists. And persistent and imaginative data-gathering by Burkitt. Of note, speculation about a specific cause remained just that at the time of that general recognition.

When confronted with a disease that is difficult to diagnose, a diagnostician should consider that it may be something not imagined, something never recognized despite being present or never seen by anyone before. The diagnostic reasoning may remain stuck at this early stage. Does the presentation profile cohere in some familiar way? Does this patient have something that clinicians generally accept as distinct and credible? Has the illness had a commensurate impact on the patient? Each of these questions must have occurred to Burkitt because he accepted the above as a foregone conclusion and proceeded to the next step of diagnostic thinking.

Given that I have a patient with a distinct and apparently new illness, what is its nature? Here Burkitt went down a familiar and comfortable diagnosis pathway: where is the disease located? Clinicians like to think initially about gross body regions such as the head, thorax, abdomen, pelvis, limbs, and spine. Burkitt chose the head (jaws) because it accorded best with his experience with the disease. It took five years of work, a lot of it from pathologists, to change this mindset to one that could consider that perhaps the disease has no one locus but is rather multi-focal in onset or even purely a systemic disease (like, say, diabetes mellitus, type 2). Once the commitment to a localized disease was undone, work could commence on consideration of the other possibilities. Unfortunately further help, beyond the fact that it was a malignant tumour, probably a lymphoma, did not come from the usual quarter: the histopathology.

The forced reliance on the striking anatomical occurrence, particularly the location in the jaws, and the geographic constriction are typically only the preliminary ways a new disease occurrence is recognized. Luckily they were each striking enough to sustain credibility through the years until more advanced laboratory approaches provided evidence that a newly recognized disease was before them. And Burkitt had the force of person to convince the wider world that this was a new and real disease although he did not know precisely what it was.

### Summary

A new disease cannot be diagnosed in the normal way until it has been recognized as such by the medical practice community. Furthermore, a new disease is not typically

recognized by a single case: occurrence of a set of cases is normally needed. Burkitt recognized and reported both of these features. Thereafter determination of its distinctive features allowed comparison to those of all other known diseases. This comparison process is greatly simplified if the seat of the disease can be specified—which was not possible for Burkitt. However, it was enormously helpful to determine its general nature, malignancy in this case. Additionally, confirming a specific geographic limitation enabled general recognition by practitioners. The recognition and characterization of African Burkitt's lymphoma illustrates how difficult the process can be when neither the locus of the disease, nor its precise cause, are known for certain.

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