

•Tribute•

## Nasopharyngeal carcinoma in sub-Saharan Africa: a tribute to Mr. Peter Clifford

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**[Abstract]** Poorly differentiated nasopharyngeal carcinoma (NPC) is a major malignancy in certain areas of Asia. It exists also in Africa, notably among largely Arab populations in North Africa, and in “hotspots” in East Africa among “native” Africans. This article deals with the latter, as studied and defined in depth during the 1960s and 70s by the Irish-born surgeon, Peter Clifford. Through his published works, he has influenced and helped define the field of head and neck cancer as it exists in Kenya. He also did pioneering work on the African childhood malignancy, Burkitt’s lymphoma (BL). Both BL and NPC have been ultimately shown to be associated with the human herpes Epstein-Barr virus (EBV). This article is written as a tribute to Peter Clifford, focusing on his work on NPC, where he first defined the disease “hotspots” in the Kenyan Highlands, studied how best to treat the malignancy in the absence of radiotherapy, looked at possible NPC predisposing factors in the Kenyan setting, and ultimately addressed how the cancer cells interact with EBV. Peter Clifford’s pioneering work was cut short by accident. Although outside East Africa he remains largely an ‘unsung hero’ in the field, his influence has been great. It begs to be re-addressed and reconsidered.

**Key words:** head and neck neoplasm, nasopharyngeal carcinoma, Burkitt’s lymphoma, Epstein-Barr virus (EBV), NPC predisposing agents, Kenya

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Peter Clifford, M.B., Ch.B., M.Ch., F.R.C.S., M.D., a pioneer in the field of head and neck cancer, died of multiple sclerosis in late 2002 at the age of 81. His obituary, written jointly by a close colleague, Henry Grant, and Jayne Clifford, his wife, was published in the *Journal of Laryngology and Otology*, in 2003.<sup>1</sup> I leave it to this document to describe his remarkable career, and to others to admire, as I do, the unique talents and insights that he brought to a field still in its infancy. Cliffords seminal work on nasopharyngeal carcinoma (NPC), and the B-cell malignancy Burkitts lymphoma (BL), was carried out in sub-Saharan East Africa, mainly in Nairobi Kenya, where he worked as an oncologist and surgeon throughout the 1960s and into the 1970s. Nowhere else does one see these diseases so vividly described nor well documented as in his papers. I write this article as a mark of appreciation of the insight and volume of information Clifford provided in a career cut short by accident, also to introduce this remarkable man and his achievements to many



scientists and clinicians. His 150 or so publications are there to be studied and admired and, even today, to challenge us.

In this tribute, I focus almost entirely on Peter Clifford's work dealing with hotspots for NPC in Kenya, since this is the component of his work that seems, to me, to have been most neglected outside that country. And I wish to re-emphasize that Clifford spent only about 15 years of his working life in Africa and a serious accident cut short his productive career. He worked later on head and neck cancer in collaboration, in London, for over a decade, but here, the patients, the emphasis and of course the facilities differ widely from those found in Africa. I am stimulated to write by the fact that the name and works of Peter Clifford were notably absent among the many excellent talks and much discussion given in particular to NPC, at the

recent meeting held in Guangzhou (November, 2008) on EBV-associated malignancies. The fact that NPC remains a major cancer problem in certain regions of North and sub-Saharan Africa was not really addressed, and apparently is little recognized today outside these immediate vicinities. However, no review article on NPC (for example, see refs. 2 and 3) would be complete without due recognition of the contributions and still unanswered questions left us as legacy by Peter Clifford.

I first became aware of his name from conversations with Georg Klein and Tomas Lindahl, in Sweden, shortly after I began my own work in the EBV field, in the early 1980s. Over time, as I became more familiar with the early literature in the field, I increasingly encountered Clifford's name prominently on papers dealing with EBV and malignancy. I tacitly assumed his

"non-existence" until Georg came to London some ten years later, and said on this visit that he would be contacting Peter Clifford. I, however, did not instigate a meeting with Peter until 1997, by which time I had traveled on a number of occasions to both China and Africa, and wanted to meet and talk with this pioneer who had worked on both NPC and BL. It proved a most enlightening encounter which is why I repeat part of a conversation from those occasions. By telephone, I had initially arranged a luncheon meeting with Peter Clifford and he asked that his wife be included also. Later I could understand the reason for this request. Peter also suggested a venue to include "being of easy access for his home in London, and having a ramp". This was the first time I became aware of the considerable physical disability that had been imposed on this impressive man. He came in a wheelchair. One of

my lead questions to him on this first occasion was, “Mr. Clifford, in your work in Kenya, did you encounter more Burkitts lymphoma or nasopharyngeal carcinoma”? He paused, then said “Let me think”. Naively, I had expected him to say - like predictably most other people in the general field would - “Burkitts lymphoma”. In Sweden I had heard that most of the lymphoma cell lines created there, such as Daudi, from African patients had come from biopsies demanding immediate attention, in parcels from Clifford. But thats not what Peter Clifford said. He said rather, “nasopharyngeal carcinoma.” I repeated this “experiment” about a year later - same restaurant, same question - having by then become fully aware of his considerable physical disability but being still rather confused by his answer. My concern was predictable, I think, since in Malawi, also in East Africa, where I have a collaborative program on BL, NPC is exceedingly rare, almost non-existent. Mr. Cliffords response, again, was first, “Let me think”. His answer, however, was initially different. He looked accusingly at me and said, “Beverly, you asked me this question last year.” My retort - not unkind I trust - was to ask for his answer, again. And it was the same. He said, hesitating slightly, “I would have said, I think, and would still say, NPC”.

Since these occasions, Peter Clifford is no longer alive, but I have had the opportunity myself to visit Kenya and check his answer. There, one finds both BL and NPC as major tumors, but in different geographical locations. It seems reasonable to assume that the older NPC population would preferentially seek the attention of a main hospital site, in Nairobi, and undertake a journey there. Doubtless too Mr. Cliffords reputation as a surgeon would have been a significant factor in attracting them, or their clinical advisors, to seek his help. The NPC hotspots, identified in his papers, are focused mainly on areas in the Kenyan Highlands, where, for example, tea exported abroad is produced. Burkitts lymphoma, on the other hand, is and remains a problem of children living around the Great Lake regions of Africa, as first noted by Denis Burkitt. My own abiding interest in NPC

still exists. For me, the question is why someone isnt exploring the relationship, if one exists, between the NPC population in the indigenous African population of East Africa and that of its cousin in Asian communities. From his keen intellect and his scientific curiosity, why did Peter Clifford himself not explore this question? A ready answer to the question may be, I think, apparent in his publications. He got diverted by BL, and a second opportunity to return to African NPC was lost in the accident that befell him. As a prominent malignancy, NPC still exists in Kenya, waiting for the same intuitive and tenacious approach adopted by Peter Clifford.

While he was alive, Peter lent me his published works, and on his death, Jayne Clifford gave me permission to keep them. These are invaluable materials, since many papers are in journals difficult to consult, such as the East African Medical Journal, not readily available in most libraries, nor freely available online. Among his numerous papers, I here only touch on those that appear to me to be the highlights among them. In line with the emphasis in the Guangzhou meeting, I restrict this list largely to those dealing with NPC in Kenya,<sup>4,46</sup> and in discussion of them, I chose those that seem to me of unique value even now. In a complete discussion of Cliffords African-related work, I would have had to include the childhood malignancy, BL, too for, after encountering Georg Klein in the mid-1960s, fully half of Peter Cliffords work, and his bibliography, deal with this topic. He worked on it in collaboration with Swedish, French and American investigators. For NPC, his sole interaction with Chinese NPC investigators appears to be via an involvement with Ho HC (refs. 29 and 31). This collaboration, and consultation with current literature on the topic, would have given him the information that would have allowed Peter to say that “no basic differences have been identified whenever a comparison between the Chinese and African versions of this malignancy have been made.” Is this still true?

Peter Cliffords first paper, entitled “Disease of the Nose and Nasal Sinuses in East Africa”,<sup>4</sup> was published in 1960 from the King George VI

Hospital in Nairobi and set the stage for his future interest and involvement in this topic. In 1964, Clifford and Beecher reviewed 95 cases of NPC,<sup>16</sup> seen over a 4-year period, and graphically described this malignancy, citing it as the commonest (29%) head and neck tumor admitted to hospital. The ratio of male:female patients seen was 5:2, with two patients under 2, seven others under 20, and the majority within 29-59 years of age. The clinical picture they describe as “differing little from that seen elsewhere in Chinese populations”, noting that it involved primarily a massive cervical glandular growth, generally without cranial nerve lesions. In Kenya, at that time a country of about 8.5 million people, none of the cases came from its European population (0.5 million), only two came from an Asian (Indian) population (of 0.25 million) and the rest came from African natives. Of these, all patients came from three (Bantus, Nilotic, Nilo-Hamitic) of the four ethnic groups, with none from the Hamitic tribes (an African branch of the Caucasian family). Thus, as among Chinese NPCs, the African malignancy involved also a possible restriction in terms of genetic origins.

Later studies by Clifford and English colleagues, delving further into the topic of susceptibility, showed that although the greatest number of cases appeared to come from the numerically majority Bantu tribe, there were no obvious hormonal differences among individuals or tribes to account for the disease.<sup>23-26</sup> The authors concluded that as most cases came from the higher altitude, colder regions of Kenya, there was probably, however, an environmental component to NPC, but some etiological contributor to the disease might still be hormones, since this would allow for the observed frequency differences between the sexes, also possibly for tribal constraints. In summarizing work on this topic, Bulbrook et al., in the 1968 book “Cancer in Africa” (by Clifford, Linsell and Timms) concluded that “the investigations into the role of the hormones in the etiology of cancer of the nasopharynx have answered few questions but rather have raised a host of new ones”. Interestingly, some hormonal

differences were indeed observed between healthy individuals and patients with cancer. This topic was reviewed later by Clifford.<sup>36</sup> He proposed that language barriers and different social customs that maintained the ethnical divisions seen among the tribes might still prove to be of relevance, but the chief predisposing elements, apparently, remained unknown. Of interest, recent events in Kenya reinforce the still-existing differences among Kenyan tribes some 40 years later. Interest in this topic has not apparently been followed-up, however. Studies examining differences in trace elements assumed in the soil were also explored with regard to NPC, but not shown to be contributing factors either.<sup>28</sup> Environmental factors associated with the higher altitudes in Kenya were not, however, ruled out in these studies, and in Cliffords opinion, must exist.

Whilst these basic studies were being carried out, Peter Cliffords other main focus was developing methods to treat NPC. In studies that were begun as early as in 1961<sup>5</sup> and continued throughout the 1960s and into the 1970s, Clifford and colleagues had concluded that whereas surgery had no place in the treatment of NPC, radiotherapy was not yet available in Kenya, and chemotherapy was suitable only for patients in hospital. With nothing better, this left nitrogen mustard as the preferred treatment. A detailed assessment of nitrogen mustard treatment with numerous case reports was the subject of a large paper in the British Journal of Cancer in 1965,<sup>19</sup> and this topic was further considered alongside treatment with chemotherapy or immunotherapy by Clifford et al. in “Cancer in Africa”.<sup>28</sup> As noted there, many of the problems associated with treatment in Kenya resulted from the fact that most patients arrived in hospital only when the disease was far advanced, a situation that apparently still exists in Kenya.<sup>42</sup>

In 1966, a paper appeared in the Proceedings of the National Academy of Sciences (U.S.A.) which, in retrospect, proved to be more prescient than was probably appreciated at the time. Based on its title, “Precipitating antibody in human serum to an antigen present in cultured Burkitts lymphoma”, and the recent discovery of the presence of EBV in BL, the findings focused on



the B-cell malignancy.<sup>22</sup> Yet, as was clearly stated and illustrated in the article, in the immunodiffusion (Ouchterlony) assay, antigens that gave positive reactions came from African BL patients (31/55), or alternatively, from Kenyan and American patients (33/39) with carcinoma of the postnasal space. This appears to be the first evidence in support of an infectious agent that associates with NPC, and possibly identified it as the same agent (that is, EBV) as that which associates with BL. Similar studies on this topic were carried out in a further series of experiments, as illustrated for NPC, giving related and supportive findings.<sup>29-34,42</sup> The African NPCs expressed various antibodies associated with the human herpesvirus, EBV, including those associated with early and capsid antigens. It is unclear whether infectious particles are being actively expressed at some stages during tumorigenesis, and if so, when. Among the papers examining the expression of antibodies related to EBV in NPC is one that notes a difference between Chinese- and African-derived malignancies. In this blinded study,<sup>31</sup> sera from East African and Chinese NPCs were titrated for antibodies to EBV using an indirect immunofluorescence technique; 84% had high titers (1:160; geographical mean level 1:348). But, whereas among the Chinese (including Hong Kong), serial sera from NPC patients, as the disease progressed, showed successive increases in the incidence of high anti-EBV titers and geometric mean levels, in the African cases the titers remained essentially constant over time, independent of tumor progression. (The latter finding had previously also been observed in serial samplings of African BL patients.) In the study cited,<sup>31</sup> elevated anti-EBV titers were not observed in other head and neck tumors, nor in controls. Such data were used then to disqualify some patients from the study, that is, diagnostically for defining NPC. The authors suggested that the apparent constancy of anti-EBV titers in the African NPC patients might be related to a reduction over time in the cancer cell population, and noted that further horizontal studies on this topic were in progress to assess this possibility. I cannot see among the

papers available to me, however, that such studies were ever published. Notably, however, subsequent findings from numerous sources confirm the unique association of EBV with undifferentiated NPCs.

It seems relevant at this point to acknowledge the input of Georg Klein and other Swedish collaborators on work concerned with serological studies on EBV and NPC, as well as to the work by Mr. Clifford in Kenya on BL, largely omitted in this tribute. On the other hand, it seems likely that the honor awarded in 1971 to Peter Clifford, an Honorary Doctorate of Medicine by the Karolinska Institute, Stockholm, the only foreigner so-honored that year, may have been largely stimulated by his contribution to BL. This degree leads me to comment on the fact that Peter Clifford, as far as I know, even with his F.R.C.S. and M.D. (hon.), preferred to be addressed, as British surgeons do, as Mr. Clifford. Thus I use Mr. instead of Dr. for him, in my title. To non-British readers, this may seem unusual.

Overall, the serological data as discussed in the papers<sup>29-34,41,42</sup> support an association between EBV and NPC (and BL) but, although unlikely, did not rule out a causal persistent infection of tumors by persistent endogenous virus. The definitive work on EBV must be attributed to zur Hausen and Schulte-Holthausen who had previously established a DNA-DNA hybridization protocol using <sup>3</sup>H-labelled EBV DNA, and applied this technique to examine tumor materials from Kenyan NPC patients (also BL patients and controls), in collaboration with Peter Clifford and others.<sup>35</sup> Their protocol produced quantitative data on the viral levels among and between tumor populations. Briefly, their findings showed varying but comparable EBV levels in NPC and BL patients, and in both cases, although levels varied among patients, they were higher in these particular malignancies than in any others tested. zur Hausen et al. concluded that the data “provided direct evidence for the regular presence of EBV nucleic acid in biopsies” of these two distinct tumor types, conclusions which have stood the test of time.

After this very active period on NPC in the

first half of the 1970s, whereas Clifford wrote an incisive review considering a role for carcinogens in this malignancy,<sup>43</sup> as well as a surgically-orientated paper focused on repairing defects in patients with head and neck malignancies,<sup>44</sup> his non-clinical attentions had apparently largely been occupied by BL. He did, however, look briefly into the possibilities of radiation for treatment of NPC in Kenya.<sup>45</sup> In his "Prospectives in Head and Neck Oncology",<sup>46</sup> given at the Twentieth Annual James Yearsley Memorial Lecture at the Royal Society of Medicine in London, in 1974, Clifford explored the broader subject, and focused less on NPC. This presentation includes other topics such as Ewings and Wilms tumors, embryonal rhabdomyosarcoma and osteogenic sarcoma, considering both the different target cells and treatment protocols. Although he took his illustrations from African patients, his lecture was not focused on them. He ended this presentation with what may prove a particularly prescient statement, noting that "with treatments restricted to chemotherapy, or chemotherapy with radiotherapy treatment protocols, a small number of cancer cells may remain viable because of pharmacological barriers, inherent or acquired drug resistance or because environmental factors provide protection against the effects of irradiation and chemotherapy" and that "the elimination of the small residual tumor cell population is most likely to be successfully managed by a competent immunological system"

Reviewing Cliffords publications during the mid 1970s, there is a decided apparent diminution in the attention he gave to NPC as compared with that he gave to BL. Whether this involved the realization that for sub-Saharan Africa as a whole, BL was proved to be more numerically relevant than NPC, whether his dominant interest in treatment seemed more likely to be served in pursuing BL than NPC, or whether the attention given by colleagues to BL to the apparent neglect of NPC was a dominant factor, we shall perhaps never know. What we do know is that briefly his focus seemed to change. And perhaps for Kenya that has proved unfortunate, for there today the NPC problem

still exists, and needs the attention that it gets only sporadically.<sup>47,48</sup>

For what appears to be the last ten years of his active professional life, Clifford, together with a cohort of collaborators, practiced his surgical and intuitive skills on diseases associated with head and neck cancers in an English setting, far away from the earlier, seminal African work. After a car accident in 1980, from which he never fully recovered, clearly he maintained a dominant interest in head and neck cancer, as the publications testify.<sup>49-62</sup> But, of course, his patients and resources both differed dramatically. Peter Clifford continued to live in London but go regularly to South Africa. He attended lectures and to talk with colleagues and, to the end, alerted and interested, but his active scientific career ended in 1985, 25 years after it began.

Reference (62) appears to be his last paper, published jointly with the British surgeon, Henry Grant, the coeditor of his obituary. My copy of this paper has a handwritten salutation from the latter to his mentor saying, "Peter. Bon Voyage! That, I think, is a suitable epitaph for a remarkable scientist and clinician.

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