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Mapping the methodologies of Burkitt lymphoma

Brendan Clarke*

Department of Science and Technology Studies, University College London, Gower Street, London WC1E 6BT, UK

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ABSTRACT

While recent accounts have emphasised the planned, large-scale and systematic character of cancer virus research in the mid-C20, I argue here that a distinctive kind of small-scale scientific research existed, and made a distinctive contribution to the development of the field as a whole. Using the case of the research carried out to understand the causes of Burkitt lymphoma in Africa during the 1960s, I highlight two distinctive practices—geographical mapping and the re-purposing of existing disease infrastructure—that played a central role in this episode. My intention here is threefold: first, I will argue that this research is unlike the research practices usually identified as typical 'big science' research concerning cancer viruses, particularly in the United States. Second, I will argue that this kind of research is also clearly distinct from the kind of research that Derek Price (Price, 1963) characterised as 'little science'. Thirdly, I will sketch a positive characterisation of this kind of research as 'small science'. I conclude by suggesting that this characterisation may be applied to other kinds of historical biomedical research, and that so doing may offer the pluralist a useful alternative way of understanding medical research in the twentieth century.

1. Introduction

Historical interest in viruses and cancer has grown steadily over the last few years. Perhaps this is unsurprising: cancer virus research played a prominent role in the development of laboratory medicine in the twentieth century. This role of cancer virus research within major biomedical research programmes (particularly in the USA) has been developed in work that tends to emphasise its planned and institutional character. For example, cancer virus research may be discussed in the context of major planned research efforts (Gaudillière, 1998; Scheffler, 2014), in the institutional interactions between biomedical research establishments and other quasi-governmental institutions, such as prisons (Stark & Campbell, 2014), or as contributor to research in other fields, such as molecular biology (Gaudillière, 1998). As John Pickstone points out, this alignment of the historiography of cancer virus research largely along institutional lines is of a piece with other social histories of medicine, where both the form of the work and the intensions of the historian have largely been imported from other contexts. Particularly important in this regard are "sociological histories of modernisation and industrialisation" (Pickstone, 2012: 239) which acted as important intellectual drivers of the development of social history of medicine in the late twentieth century (reviewed in Porter, 1995).

This is not to say that cancer virus research itself (as scientific practice) was confined to large research institutions. As the other papers in this issue also relate, the actual practices that contributed to tumour virology research in the later twentieth century were exceptionally polymorphous. This paper will sketch out one group of research that does not align with the dominant narrative of centralised science, and one that is thus not so clearly visible through the usual historiographical optics. Its aim therefore is to focus on research work occurring at a rather small scale. Important too is that this work occurred outside the United States, placing the practices reviewed here at further geographical remove from the big medicine of (for example) the National Cancer Institute.

* Tel.: +44 (0) 2076797132.
E-mail address: b.clarke@ucl.ac.uk.

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This paper characterises a very particular kind of research in tumour virology, and it does this via the case of Burkitt lymphoma (BL hence) in Equatorial Africa between 1950 and 1970. While many historical accounts of these events have been given before (Evans, 1993; Glemser, 1971; zur Hausen, 2006; Hutt, 1981), they are firmly aligned with a historical tradition that Stark and Campbell characterise as "organized searches for causes, therapeutics, and preventions" (2014: 218). While this paper will discuss just such a search for causes and prevention, my emphasis here is on the means by which these goals were sought, rather than the details of the causes or prevention strategies that were eventually found. I have selected two kinds of research work for special attention. First is the group of geographical research practices used to investigate the aetiology of BL during the 1960s. While these have previously been described as romantic adventure stories of derring-do in the tropics (Glemser, 1971), my intention here is to understand them more in terms of the growing interest in the history of science community of understanding the geography of the production of scientific knowledge. This alternative means of describing the role of place—described as the 'geographical turn' in the history of science by Finnegan (2008: 369)—in part consists of a greater attention to the role played by location in conditioning the character of scientific activity. In this essay, I therefore aim to pick out some of the geographical techniques employed in this case, and to demonstrate how these techniques shaped ideas about the nature and causation of BL.

Second, I have picked out a number of examples where existing research infrastructure—particularly that put in place to conduct malaria research—became reused by researchers interested in BL. Each of these two studies is intended to reflect in more detail my historiographical middle-way. In turn, this should serve as a corrective to the prevailing historical interpretation of the search for cancer viruses. While planned, managed, or centralised research was an important part of the field (see, for that, Scheffler's paper 2014), it was not constitutive of it. Epistemologically and practically distinctive things happened in the intellectual cracks and corners, and these played a key role in shaping the much more visible big science of national institutions. Yet these practices, which I refer to below as *small science*, have been poorly served by this emphasis on centralisation, planning and management.

The structure of this paper will be as follows. In Section 2, I give an outline of research conducted on Burkitt lymphoma in Africa between 1950 and 1970. I then develop two areas of this research in more detail. The first of these, discussed in Section 3, is the role of maps and mapping practices, and their interactions with other research practices, while in Section 4, I deal with the re-use of research infrastructure to investigate this disease. I then move to more conceptual territory in Section 5, where I characterise (in fairly general terms) small science, and briefly hold up certain aspects of the BL case as useful illustrations of this kind of scientific practice.

2. Burkitt lymphoma

This case deals with research conducted between 1950 and 1970 on BL, a tumour syndrome caused by infection with Epstein–Barr Virus (EBV). EBV has a world-wide distribution, and is associated with the development of a range of malignant and non-malignant conditions (Deyrup, 2008). While up to 90% of adults show evidence of prior infection (Henle et al., 1969), the development of malignant disease is rather rare in the developed world, where infection manifests most usually as infectious mononucleosis (glandular fever). However, in combination with environmental factors found in the tropics, the virus can contribute to the development of BL, which is a highly malignant and rapidly progressive extranodal B-cell lymphoma.[1] This cancer mainly affects children, and has a number of unusual clinical features, such as its predilection for anatomical sites not usually associated with malignancy, such as the bones of the jaws.

A very brief account of the clinical (rather than laboratory) research performed on this disease is as follows: the strangely high incidence of jaw tumours of atypical appearance in children was reported several times in Equatorial East Africa during the first half of the twentieth century.[2] These were usually regarded more as curiosities than viable targets of research:

> *His face was massively swollen, with bizarre lesions involving both sides of his upper and lower jaws. I had never seen anything like it. The teeth were loose and the features grossly distorted. If a single jaw quadrant had been involved, I might have considered it to be an infective process such as osteomyelitis, but not with all four quadrants affected. This unusual distribution also seemed to rule out any form of neoplasia. Results of the biopsy had suggested some form of granuloma. I was totally baffled, but photographed the child and considered this to be another of the curiosities one had to become accustomed to seeing from time to time in Africa.*
>
> (Burkitt, 1983, 1777)

However, further encounters with other children with similar symptoms rapidly changed the status of these curiosities. Not only did other children have massive, characteristic tumours in the jaws, they also had distinctive abdominal tumours. This combination of tumours in the jaws and at multiple sites in the abdomen arising simultaneously suggested the operation of some altogether unknown disease mechanism. Further research (see Burkitt, 1983; Clarke, 2011; Hutt, 1981) revealed that, far from being occasional oddities, cases of this tumour syndrome were alarmingly common in Uganda. Early descriptions of the syndrome (Burkitt, 1958; Burkitt & O'Conor, 1961; O'Conor, 1961; O'Conor & Davies, 1960) gave clinical, epidemiological, pathological and histopathological features. Of particular note was that the tumour syndrome was caused by some kind of extranodal lymphoma; that the disease was geographically confined to an East-West belt across Equatorial Africa; and that the incidence rate was extremely high in localised areas within this lymphoma belt. Rather than being an isolated oddity, it appeared instead that a very common cancer had been hidden in plain sight. As the manifestations of the disease were not subtle—instead florid, progressive, and fatal—the fact that so little attention had been paid to isolated cases of the disease was somewhat mysterious:

[1] The means by which EBV causes a range of diseases depending on context is complicated, and the technical details go far beyond the scope of this essay. In very general terms, though, it appears to be the case that infection with EBV interacts with other agents to promote the development of chromosomal abnormalities (particularly translocations), and it is these that bring about malignant disease. Unlike other tumour viruses, such as human papillomavirus, where infection with different strains of the virus manifest as different types of cancer, the link between EBV and human disease seems highly multifactorial, with different combinations of virus plus other causal factors leading to different diseases. For details of these in relation to EBV, see Thorley-Lawson & Allday (2008).

[2] Some of these reports were widely disseminated. For example, there was a clinical meeting in the Mulago hospital in Uganda in October 1955, proceedings of which were published as a short article entitled 'Tumours of the Jaw' on the 29th exists, at which Burkitt was present (Singh, 1955). In this note, the higher incidence of jaw tumours at Mulago than in either Europe or America was noted (Singh, 1955, 70). Other reports from Uganda at the turn of the century were also known (Davies et al., 1964; Hutt, 1981, 762).

> *"It was the recognition that many unusual and hitherto unconnected tumours were, in fact, but different manifestations of one tumour syndrome that initiated investigation of the problem as a whole."*
>
> (Burkitt, 1962d, 75–6)

It is no surprise that a discovery of a new kind of cancer would prompt many questions. Those asked during the early stages of BL research can be conveniently grouped into four kinds—questions as to the nature of the clinical condition, questions as to its aetiology, questions concerning possible therapeutic strategies, and questions about prevention. My focus in what follows is on the first two of these questions: those of the nature of the syndrome, and of its possible causes.[3] While the disease itself was an unusual one—occurring at unusual anatomical sites apparently simultaneously, highly aggressive, and affecting demographic groups not commonly afflicted by cancers—giving a partial clinical description appeared to have been neither controversial nor difficult. Burkitt's first publication about the disease (Burkitt, 1958) contains a detailed description of the clinical features of this disease, including information about demographics, geography, clinical features, histology, and treatment. This was based on the description of 38 individual cases between 1951 and 1958. Throughout, each of these cases is presented as examples of a single malignant disease: cancer because of its histological appearance, a unified disease because of the characteristic clinical appearance. However, despite the certainty with which these descriptions were made, much about the syndrome remained unknown. Most importantly, as Burkitt identified "Although the clinical picture of this sarcoma is easily recognized, its site of origin and nature remain obscure." (Burkitt, 1958: 221).

Here, then, giving a clinical description did not require an understanding of the aetiology of the disease. Instead, this description of clinical features appeared to pose a series of baffling aetiological problems. For example, the kinds of pathological processes responsible for the geography of this syndrome appeared extremely obscure. Why did this disease appear to occur almost exclusively in central Africa?

3. Maps

To see maps just as tools of communication, or as a ways of presenting established findings, is to mistake their role in permitting and shaping research. This should not be a particularly shocking claim from either the historical or philosophical side (Hess & Mendelsohn, 2010; Livingstone, 1993; Morrison & Morgan, 1999). Rather than pushing at this open door, I will instead tend towards the illustrative, by emphasising how the construction and use of maps shaped research on BL. One root of geographical research in this case is to be found in Burkitt's biography and bibliography. An obituarist describes a "lifelong passion for plotting things on maps" (Heaton, 1993, pp. 951). His later work, on dietary fibre and its link to diseases of the developed world, also came, in part, from work on geographic pathology. There too was a family connection: his father, "an Irish surveyor and naturalist, who invented the ringing of birds to plot their territories." (Heaton, 1993, pp. 951). Burkitt's pre-BL research also showed an interest in working at the intersection of the geographical and the pathological, including geographical variation in the rates of testicular hydrocele (Burkitt, 1951) and subcutaneous phycomycosis (Burkitt, Wilson, & Jelliffe, 1964).

The first steps in BL geographical research arose at the intersection of two anomalous geographical features of the tumour syndrome. First, despite being so very striking in appearance, the disease did not seem to have been previously described. Was it the case that this apparent failure of observation was a global phenomenon, or a local one? In other words, was it the case that the disease, occurring everywhere, had been missed everywhere? Alternatively, perhaps the syndrome was geographically restricted in distribution, and the omission was more local. Either result would prompt a rather different research programme, particularly because the identification of geographical differences in aetiological factors would presumably be a necessary part of any effort to try and understand the causes of the condition. Early anecdotal reports from South Africa reporting the apparent absence of the lymphoma syndrome there seemed to suggest that the failure of detection was indeed local, implying that some geographical calculus of causes would be required. Second, very early in research, Burkitt noticed local (i.e. within Uganda) geographical differences in numbers of cases (Burkitt, 1983, pp. 1778–9). Again, it was not clear which conclusions could be drawn from this finding. While "far more cases were being referred from the northern and eastern areas" of Uganda (Burkitt, 1983, pp. 1778), it was also true that other features of the population of these regions were capable of accounting for this difference: the population density was much higher, and transport to the University hospital in Kampala was far easier.

Burkitt investigated these two geographical problems by means of a postal survey, in which health workers throughout Africa were asked to report the appearance of cases (Burkitt, 1983, pp. 1779). Further research by literature survey and personal correspondence indicated that Africa was the only region where this tumour was found with any degree of regularity (Burkitt & Wright, 1963, pp. 69–70), although other locations where the disease would later emerge—particularly in Western Papua New Guinea. By mapping the medical centres from which cases had been reported, Burkitt discovered that the disease was essentially confined to a sharply demarcated region of Equatorial Africa, which became known as the lymphoma belt (Burkitt & Wright, 1963: 103–13). Once constructed, this fairly crude map was then interrogated in some rather interesting ways to determine how this lymphoma belt might be distinguished from its surroundings. What here was making the difference between areas of high and low BL incidence?

Very early in the project, it was noted that it would be possible to account for the geographical distribution of the syndrome in terms of climate factors (Burkitt & Wright, 1963):

[3] The relationship between these different questions is a most interesting one. I had previously assumed that these questions would sequentially depend on one another. Being able to give at least a partial clinical description of a disease seemed to me to be a necessary component of understanding the aetiology of that disease. In turn, knowing the causes of a disease seemed similarly necessary to provide an effective treatment or prevention of it. This assumption was mirrored by the usual answers to questions about the reasons for seeking causes in general terms, in that causal knowledge should leave the user able to explain, predict, and control that system (Casini, Illari, Russo, & Williamson, 2011). This case seems to require some correction of this view of the relationship between these different questions. As shown in Section 3, questions about the nature of the disease continued to interact with questions about its aetiology for long enough that this assumption should be questioned. It is also illuminating to note that the second pair of questions—concerning therapy and prevention—differ from one another in their respective dependence on causal knowledge about aetiology. In this case, prevention strategies certainly do seem to require some earlier causal knowledge about aetiology, although an effective vaccine against EBV still proves elusive (Cohen, Mocarski, Raab-Traub, Corey, & Nabel, 2013). Therapeutic strategies, on the other hand, did not require aetiological knowledge in the same way, and well before EBV was accepted as causing the disease, a fairly successful treatment programme using cytotoxic agents was in place (Clifford, 1970).

> *"…if he took a map of Africa and eliminated all areas where the mean temperature fell below 60 degrees F. at any time of year, areas over 5,000 feet in altitude, and areas where the mean rainfall of the year fell below 30 inches, he could produce a map which is almost identical with the map of tumour distribution. This suggests that the type of vegetation (being dependent on rainfall) and the temperature are two major factors determining the distribution of this tumour."*
>
> (Burkitt, 1961, pp. 512–3)

Finding that the syndrome was largely confined to these low-lying, warm, and wet areas, and that these conditions matched those favoured by many disease-transmitting insects, Burkitt produced similar comparative maps which compared the distribution of the tumour to the distribution of several prevalent arthropods known to be disease vectors. Two of these—tsetse (*Glossina* spp.), and *Anopheles* mosquitoes—were an extremely good fit to the lymphoma belt (Burkitt & Wright, 1963, pp. 131–2). In the second case, a recent outbreak of another *Anopheles*-transmitted disease—O'Nyong–Nyong fever—with a similarly distribution apparently limited by climate, acted as further evidence implicating the mosquito. From these analogous cases:

> *From what has been found out so far about this tumour one cannot but be impressed with the resemblance this has to some of the virus induced tumours of mammals and cannot avoid wondering if this might not be a virus induced tumour of African children…It would appear that there is a prima facie case for investigating this possibility.*
>
> (Burkitt & Davies, 1961, pp. 369)

Unfortunately the authors are not explicit at this point regarding which virus induced tumours of mammals they mean. However, other sources (e.g. Burkitt & Wright, 1963: 135) suggest that polyoma virus infections in rodents produced a superficially similar clinical syndrome (Stewart, 1955).

Regional investigations of the distribution of the disease as a whole were matched with a programme of more local geographical research. Three researchers (Denis Burkitt, Ted Williams and Clifford Nelson), packed into a battered Ford station wagon, visited 56 medical centres across eight countries on the south-eastern tail of the lymphoma belt during late 1961 (Burkitt, 1962c; Burkitt & Wright, 1963, pp. 113ff). Dubbed the "tumour safari", the intention was to visit medical units straddling the borders of the lymphoma belt to attempt to sharpen the lines of demarcation between tumour-bearing regions and non-tumour bearing ones.[4] Here, the initial mapping of tumour cases was used to plan the route of the safari, as shown in Fig. 1 (Burkitt, 1962c, pp. 381). In turn, the distribution shown on this initial map was refined and corrected during the safari by tracing cases occurring at the margins of the belt to their originating locality, rather than to the medical centre from which they had been reported (Burkitt, 1962c, pp. 381). Other features of the distribution—such as its suspected dependence on climatic factors—were also investigated, by showing, for example, that local tumour incidence appeared to vary with altitude and minimum temperature (Burkitt, 1962c, pp. 385–6).

A more global interaction between maps and other research methods was also in play during the early 1960s. A set of

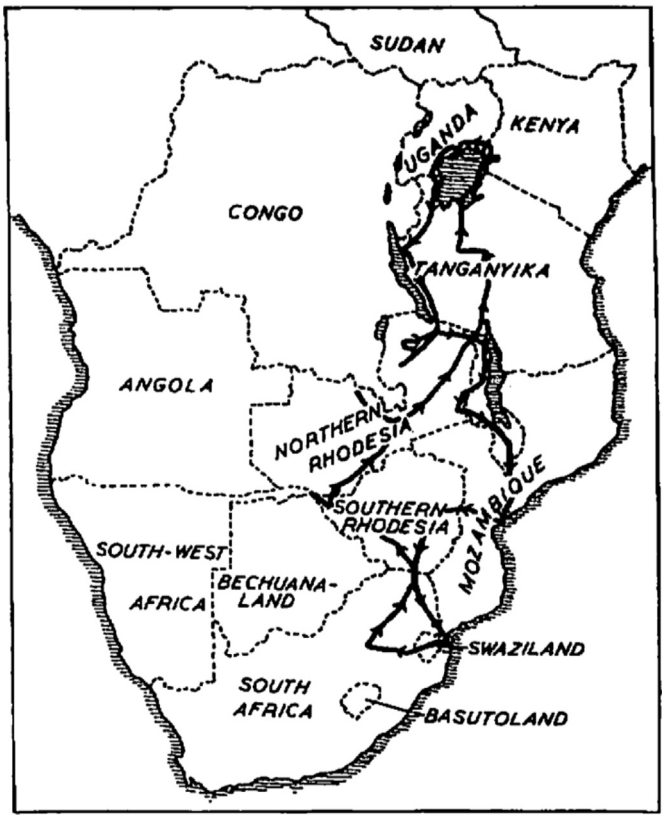

Fig. 1. Route of the tumour safari. Reproduced with permission from Burkitt (1962c, p. 381).
Reprinted by permission from Macmillan Publishers Ltd on behalf of Cancer Research UK: British Journal of Cancer. Burkitt, D. "A 'Tumour Safari' in East and Central Africa." *British Journal of Cancer*, 16(3): 379–86, copyright 1962.

comparisons of incidence rates of various cancers in various contexts was part of early BL research. This was carried out in Uganda from 1951 by the Kampala Cancer survey (O'Conor & Davies, 1960, 527), which collected data from cases of cancer admitted to hospitals in the Ugandan capital. While difficulties in data interpretation—such as uncertainty surrounding the size of the population from which this data was collected (O'Conor & Davies, 1960, pp. 528)—these authors attempted to draw a number of conclusions about the kinds of childhood cancer seen in Uganda. Most strikingly, the relative rates of both leukaemia and lymphoma were very different in Uganda when compared to other geographical contexts.[5] Leukaemia was much more common than lymphoma both in the developed world (O'Conor & Davies, 1960, pp. 528–9), and in regions of Africa outside the lymphoma belt (Higginson & Oettlé, 1960, pp. 651–3). However, this relation was reversed: within Uganda, lymphoma much more common, and

[4] This unusual method was explained via a pathological analogy "This exercise would be comparable to the pathologists choice of marginal tissue for detailed histological examination of any lesion." (Burkitt, 1962c, pp. 380).

[5] It is worth clarifying the terminology at this point. Leukaemia and lymphoma are both malignant tumours of blood cells. Lymphomas are solid tumours, while leukaemia exists in a distributed form in the blood and bone marrow. Lymphoma and leukaemia may also differ in the kinds of blood cell from which they originate. As the name might suggest, lymphoma comes from malignant change affecting lymphocytes or lymphocyte precursor cells. Leukaemia may originate from lymphoid cells too, in which case the disease is called lymphoid leukaemia. Alternatively, leukaemia may come about from the myeloid cell lines that usually give rise to red blood cells and non-lymphoid immune blood cells. This kind of leukaemia is called myeloid leukaemia. For an overview of this classification in more detail, see Harris et al. (1999).

leukaemia much less common, than in much of the rest of the world (O'Conor & Davies 1960).[6] The authors noted:

> *Since malignant lymphoma in this study has replaced lymphatic leukaemia as the most common neoplasm of childhood, it is suggested that this may represent a true variation in the site of malignant proliferation and, more important, an alteration in the natural history and course of the diseases of the lymphopoietic system.*
>
> (O'Conor & Davies, 1960, pp. 529)

This suggestion was followed by others researching cancers in Africa. For example, in a report on lymphoma in Kenya carried out in collaboration between the Sloan-Kettering Institute in New York and the Medical Research Laboratory in Nairobi, similar claims were made for the reciprocal relationship between leukaemia and lymphoma:

> *Study of the lymphomas of African children has led to the observation that these may well be simply a different expression of childhood lymphoma which in North America usually manifests itself as acute leukaemia.*
>
> (Dalldorf, 1962, pp. 1028)

In other words, this inversion of the expected ratio of leukaemia and lymphoma cases within the belt led to the suspicion that lymphoma syndrome was perhaps an unusual manifestation of lymphoblastic leukaemia. If this was true, and given the interest in finding an infectious aetiology for leukaemia in the United States (Scheffler, 2014), it suggested that BL too might be caused by a virus of some kind. In concert with the other evidence, it suggested that the syndrome might be due to an arthropod-vectored virus (Burkitt, 1962a, 234; Burkitt, 1962b, 217–9; Burkitt, 1962d, 77).

These very active roles played by maps and mapping practices in research suggest that they played an epistemic role in this programme akin to those roles of *models* of scientific systems (De Chadarevian & Hopwood, 2004; Morrison & Morgan, 1999). Broadly, models are devices that can be used to understand target systems by representing certain aspects of that target system. An example of this clarifying power of representation is the map of BL cases produced by Burkitt. Representing one aspect of many particular cases of the disease—their geographically location—drew out an important feature of BL as a whole. This "partial representation" (Morrison & Morgan, 1999, p. 27) of the disease was used as evidence when trying to understand other aspects of BL, such as its relationship with leukaemia. These maps were built from evidence (here, the geographical locations of each case of BL), and then used as evidence (that the syndrome was geographically restricted) when substantiating causal claims regarding the aetiology of BL. This embedding of these particular maps in the context of African BL research suggests that they fulfilled similar roles to other kinds of models in very different biomedical contexts, such as the chromosome maps used as research models in *Drosophila* genetics (Kohler, 1994), which similarly represented some (but not all) of what was understood about particular chromosomal loci. These interactions—between maps and research, and research and maps—differ from the conceptual claims drawn about maps in much of biogeography. For example, in a recent book (2011, p. 5), the biogeographer Tom Koch argues that "maps present the discrete elements of an epidemic or pandemic occurrence…as a unified event." While maps did serve similar roles in this case, such as aggregating the disparate cases of the lymphoma syndrome into a unified 'lymphoma belt', they played many other roles too. Here, far from stripping away the properties of the things plotted, in this case, new means of producing evidence (e.g. geographical comparisons) emerged from the production and investigation of maps. This production made apparent phenomena that had previously remained hidden within alternative conceptual structures of inquiry.

For some researchers involved in this project, the development of these mapping practices themselves was to remain a focus of inquiry. Burkitt, for example, continued to research both the geographical aspects of particular diseases (for instance, work on dietary fibre and bowel disease in Burkitt, Walker, & Painter, 1972), and the conceptual features of disease geography. This included work on the role of geographical studies in malignant diseases in general (Burkitt, 1965); the role of comparative geographical studies of disease (Burkitt, 1969, 1970) in understanding disease causation; the special role played by geographical methods in investigating disease peculiar to particular tribal groups (Burkitt, 1969); and the role played by mapping in understanding disease outbreaks that cross national borders (Burkitt, 1968).

4. Mosquitoes

A second evidential feature of this case developed through the reuse of existing research infrastructure. While several different examples of this are to be found in the literature, by far the most common was the re-purposing of tools and techniques intended to investigate and control malaria, a disease of major public health importance in the contexts where Burkitt lymphoma was found. For example, as malaria is transmitted by *Anopheles* mosquitoes, regular counts of these insects were performed in many districts, in part to gauge the impact of mosquito-suppression measures. This work on the vector (the mosquito) was matched to a surveillance programme on the disease itself. This had two wings: surveillance of malaria incidence (see also MARA (2010), a contemporary continuation of these African malaria surveillance programmes) and the use of opportunistic or diagnostic examinations of blood films, used to detect malaria parasites directly in individuals.

As the geographical distribution of the disease suggested that an insect vector of some kind might play a role in transmitting it, the collection of arthropods as part of the surveillance of insect-borne diseases played a critical evidential role in supporting particular claims regarding the aetiology of BL. Not least, the maps of insect distributions that resulted from this provided maps, useful when trying to understand the possible causes of the belt-like distribution of BL (as discussed in Section 3).

Similarly, blood films were extensively re-purposed to demonstrate important clinical features of the tumour syndrome. As blood-films for malaria would also effectively detect the abnormal blood cells found in leukaemia, this acted as a kind of unintentional surveillance programme, which showed that the incidence of leukaemia was very much lower than expected throughout the lymphoma belt. Incidence rates of lymphoma were also re-used from other research work, with the two main sources being the Mulago hospital pathology records (and collated during research into malignant diseases of the heart by Lothe and Somers, 1960) and the Kampala Cancer Survey (Davies, Wilson, & Knowelden,

[6] A total 125 microscopically confirmed cases of cancer in children were reported to the survey between 1951 and 1958. Of these, 7 were cases of leukaemia (5 myeloid, 2 lymphoid), while 60 were lymphomas. Of these, 57 were recorded as 'lymphosarcomas' which was the contemporary terminology for BL, while the remaining 3 were Hodgkin's lymphoma.

1958), which contained very wide-ranging and detailed information on the rates of different cancers occurring in the area of Mulago, together with comparative incidence data for the developed world. The conclusion of this was that malignant lymphoma was very much more common (by a factor of nearly four times (Lothe & Somers, 1960, pp. 160)) in Uganda than Europe. When this was combined with other data showing the high incidence of lymphomas, this inversion of the usual rates of lymphoma and leukaemia was a key piece of evidence in support of claims that a virus might cause the condition, with the further suggestion that some kind of common aetiology might be shared by this lymphoma syndrome and leukaemia, with distinct environmental factors in different geographical contexts leading to the development of one or the other.

There are many other details of this case to relate (see Clarke, 2011, pp. 25–52). Very briefly, however, the main events are as follows. Many different vectored viruses were suggested as possible causes of the tumour syndrome (reviewed in Epstein, Henle, Achong, & Barr, 1965), mainly because they were occasionally detected in biopsied tumour material. However, the accidental finding that BL cells could survive in cell culture (Epstein & Barr, 1964) lead to the detection of EBV viral particles by electron microscopy within cultured BL cells in early 1964 (Epstein, Achong, & Barr, 1964). Further characterisation of this virus led to the suspicion that it was aetiologically involved, not just in BL, but in a range of cancers (Henle & Henle, 1966a, 1966b). As regards BL specifically, it was generally accepted as being caused by EBV infection until the completion in 1978 of a prospective study involving 42 000 children in the African lymphoma belt, which showed qualitative and quantitative differences in the immune response to EBV between affected and non-affected individuals (De-Thé et al., 1978).

5. Little, small, and big sciences

Derek Price's 1963 book gave rise to what is now a venerable distinction between big and little science. However, each side of the distinction did not receive equal attention: Price's emphasis was firmly on the characteristics and implications of big science, with little science as little more than a contrast-class of methods and practices. While Price deprecating the traditional picture of "…the Little Scientist as the lone, long-haired genius, moldering in an attic or basement workshop, despised by society as a nonconformist, existing in a state of near poverty, motivated by the flame burning within him?" (Price, 1963, pp. 3), he did little to explicitly correct it, beyond some rather vague claims about the way in which little science was the antecedent of big science. This characterisation of little science, then, was primarily a negative one: little science as whatever big science was not. And big science, while a big idea, is itself a slender concept: science grows exponentially, in a logistic fashion, towards a culturally-determined saturation point. This saturation has three major implications. First, it erodes the average quality of scientific work (as more training of scientists means an increase in the recruitment of those not—for one reason or another—best suited to excel). Second, it leads to an explosion of scientific publications. Third, the cost of doing science increases dramatically. In turn, these difficulties drive the centralisation of science: large research institutions solve problems of cost; a rise in the number of authors of an average research article (Price, 1963, pp. 87–90) and the development of highly cited journals to obviate the problem of undesirably low signal-to-noise ratios caused by high volume, low average quality scientific publication; the generation of invisible colleges to avoid the journals altogether:

> *"In many ways the modern ease of transportation and the affluence of the elite scientist have replaced what used to be effected by the publication of papers. We tend now to communicate person to person instead of paper to paper. In the most active areas we diffuse knowledge through collaboration. Through select groups we seek prestige and the recognition of ourselves by our peers as approved and worthy collaborating colleagues."*
>
> (Price, 1963, pp. 90–1)

To analyse by contrast, then, little science will consist of few activities, performed by the few: an elite of highly motivated, and highly skilled, actors. Little science will be relatively inexpensive (certainly when compared to the integer-percentage-of-GDP appetites of big science). These actors will not work in large institutions, but small ones. Communication within this sparse community will be via a small number of scientific journals without evidence of the super-specialisation that is a feature of the viable big science journal. Finally, big science was (in the early 1960s) new: "a change in the state of science the like of which we have not seen for 300 years." (Price, 1963, pp. 115).

While I stress that this characterisation is a result of my own contrastive working through of Price on big science, it seems a fair fit to the historical cases that he invokes to illustrate the workings of little science. That, to me, seems sufficient for my purposes, which are to suggest that Price's distinction between big and little science is just a distinction between two kinds of scientific practice, rather than an exclusive and exhaustive dichotomy. My argument here follows a suggestion of Price's:

> "…tucked away in some academic corners, modern Big Science probably contains shoestring operations by unknown pioneers who are starting lines of research that will be of decisive interest by 1975."
>
> (Price, 1963, pp. 3)

Now even given Price's rather anaemic characterisation of little science, this activity in the gaps of big science does not appear to refer to little science. Broadly, if little science is the parent of big science, this kind of scientific built into the corners of big science research is something different, a Womble-ish contemporary.[7] For the sake of convenience, I have termed this *small science*, and my aim over the remainder of this section is to sketch a characterisation of this small science in general terms, and to give illustrative vignettes drawn from the BL case given above.

As a first point of contrast, Price argues that there is an ancestral relationship between little and big science. But while little science evolved into big science, small science is contemporary with, and complimentary to, big science. In the BL case, the claim of non-antecedence can be easily drawn. There was big science human cancer virus research happening at the same time as this small science, such as the Special Virus Cancer Program. In this case, though, the small science discussed here did not lead directly to big science research. Rather than the ancestor, small science is the contemporary of big science here. Neither should small science be regarded as some kind of primitive counterpart to big science.

[7] The Wombles were a race of fictional, furry, anthropomorphic creatures who subsisted by recycling the human detritus that they discovered on Wimbledon Common in South London. They first appeared in a series of children's books (Beresford, 2010, for example), but came to widespread prominence via a hugely popular series of television programmes for children that began broadcasting in the mid-1970s. Their motto—"Make Good Use of Bad Rubbish"—seem highly apt in describing the practices of small science.

Much BL research was highly sophisticated, such as the ingenious reuse of data collected from malaria and cancer research projects.

Next, these kinds of scientific practice can be distinguished by a differing approach to their phenomena of interest. The questions addressed by small science research aim to make sense of poorly-characterised phenomena. Here, the aim is to investigate features of the world that are poorly characterised or understood via wide-ranging and omnivorous programmes of research. Neither the problem, the necessary methods, nor the kinds of answers produced, will be known or understood at the outset of research. This kind of uncertainty can be contrasted with the (deceptive) certainty of strategies found in big-science. Here, the aims, paths and objectives of research are ostensibly well-understood before research begins. This lends a veneer of certainty regarding the phenomena in question, the methods used to research it, and the kinds of answers thrown up by this research, which is quite lacking in small science. The interaction between descriptive and aetiological questions in geographical research in the BL case is the salient example here: the description of the disease (its distribution, for example) changed, and was changed by, descriptions of possible aetiological factors (such as arthropod distributions).

These different aims, paths, and objectives of big science and small science give rise to a distinctive set of social, cultural, and epistemological values for each. These values are so ingrained into the research that small science research projects require profound translation before they can participate in the systematic and grand work found in big science. As a consequence of the uncertainty that so visibly surrounds them; the conclusions of small science research projects are often highly equivocal. These doubt-full and nuanced findings require translation or re-working before they can participate as targets or tools of inquiry in the decidedly more certain context of big science. This barrier of translation promotes the autonomous coexistence of small science in a landscape dominated by big science. While little science may be the ancestor of big science, small science projects do not grow up to become big science. They are not first steps, but independent research programmes in their own right. That is not to say that big and small sciences are isolated from one another. Instead, they are joined by networks of reciprocal connections that operate through a permeable membrane of values. For example, ideas or practices that have arisen in the sphere of big science may well circulate into, and influence, small science research, and vice versa.

My central, rather broad metaphor here is one of pollination occurring between big science and small science. In the BL case, there were several reciprocal interactions with big science-type projects, such as later prospective epidemiological and virological research. For instance, BL researchers in Africa passed much clinical and epidemiological material to laboratories in the developed world, and this material participated in virological (Epstein et al., 1964), serological (Henle & Henle, 1966a, 1966b) and epidemiological research (De-Thé et al., 1978). In turn, these researchers have led to BL and EBV being used as model systems in much other cancer virus research in the later twentieth century (Bouffet, Frappaz, Pinkerton, Favrot, & Philip, 1991).

6. Conclusion

To conclude, I suggest that the BL case does not fit neatly into Price's dichotomous classification of big and little science, but instead shares features of each. For want of a better term, I have characterised this kind of scientific practice as *small science*. As regards this quibbling with Price, my intention is modest: I have argued above that big and little science should be regarded as a reasonable way of characterising some, but not all, kinds of cancer virus research in the twentieth century. In other words, I suggest that Price's characterisation should not be interpreted as an exhaustive dichotomy. With reference to the particular case of cancer virus research discussed in detail here, characterising kinds of scientific practice in this more pluralistic way is worthwhile: there is much that is historically interesting in cancer virus research that does not fit neatly into a historiography dominated by centralised research. I argue that rather different messages emerge when the diverse parts of the BL story—big and small—are aggregated: as is so often the case, the sense of the whole is at variance with the senses of its constituent parts. If any more broad lesson is to be extracted from this aggregation—beyond the simple-minded one that a problem centred in our sights tends to look rather different from one glimpses in our peripheral vision—is should be this: not all fruitful work on viruses and cancer was planned, managed, or centralised.

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