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RESEARCH ARTICLE

African Environmental Pressures and Carcinogenesis: The Impact on The Lymphomas, the Leukemias, and Breast cancer

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ABSTRACT

The African environment has for millennia been dominated by rampant agents of infections, of which malaria is among the best known, virtually uncontrolled, and associated with lifelong human struggles, ameliorarated by measures as socioeconomicaly affordable. This has led to the emergence of a variety of genetic aberrations, some of which are deleterious, resulting in major disease dysparities, including benign ones like sickle cell disease, and malignancies like the leukaemias, lymphomas, and breast cancer. They include the reduced incidence and the absence of its peak in acute lymphoblastic leukaemia in the first quinquennium of Nigerian children, which is otherwise typically seen in the children of high-income countries. Conversely is the observation in acute myelogenous leukaemia, with its chloroma-associated variant and its incidence peaking in the second quinquennium. This epidemiology is akin to the recent observation of acute myelogenous leukemia among sickle cell disease patients among the people of African descent in California, USA. Chloroma-associated acute myelogenous leukemia, and Burkitt lymphoma are linked with low socioeconomic status, an epidemiological feature that is shared with triple negative breast cancer patients in West Africa and the women of African descent in the United States. While a role for the malaria-associated genetic aberration underlying the *Duffy null* genotype is confirmed in the diversity of the triple negative breast cancer in the women of West Africa and those of African descent in the United States, it is conceivable, but not yet established in acute myelogenous leukemia. The zoonosis-linked human T-cell lymphotropic virus type 1 infection is associated with at least 17% of non-BL-non-Hodgkin lymphoma in form of its sentinel disease, the adult T-lymphoma/leukemia, but unexpicably much lower than the 50-60% of other major endemic zones of Japan and the African descendants of the Caribeean. This report describes the clinical, laboratory, and epidemiological features of leukemia and lymphoma cases diagnosed between 1982 and 1984 in the city of Ibadan, Nigeria, some of the features of which are reminiscent of the observations of Ludwig Gross's experiments on environmental influences, such as malnutrition and infections, on animal leukemogenesis. These events are the consequences of the primordial pressures that have shaped human genetics and pathophysiology. Evidence provided in this study, indicating association of increasing socioeconomic status with increasing frequency of the *c-ALL* subtype, is indicative of the prospects for leukemogenesis of acute lymphoblastic leukemia and its epidemiology in Nigerians. Some findings reported here indicate the influence of the African genetic ancestry in the etiology of acute myelogenous leukemia, while socioecomic status is linked to the etiology of childhood acute lymphoblastic leukemia, as well as a variant of chronic lymphocytic leukemia, and the chloroma-associated acute myelogenous leukemia. These observations are suggestive of the existence of pathways to etiological discoveries in the leukemias. Observations reviewed in this paper reflect examples of changes that have occurred over the past 200 years in the societal perception of health challenges among the new-found communities of colonial Africa and the Americas - from the reductionistic connotations such as in the "virgin-soil theory" - towards that of social determinants of health.

Introduction

The discovery in1958 of Burkitt lymphoma (BL) and the linkage of its cause to the African environment was a landmark event in the history of cancer research.[1] Together with his colleagues, Denis Burkitt, the missionary surgeon in Uganda, undertook one of his field geographical surveys and visited more than 60 hospitals in Eastern and Southern Africa to examine the occurrence of the disease, and found it to be correlated with the same temperature and rainforest zones as malaria. This Burkitt lymphoma survey is regarded as one of the pioneering studies of geographical pathology, in which the environment consisted of rain forests extensively infested with malaria parasite-carrying mosquitoes.[2] The discovery of Burkitt lymphoma subsequently changed the cancer narrative forever, especially as it led to the discovery of the Epstein-Barr virus in 1963. The latter discovery itself was the sequela of an encounter between Denis Burkitt, the so-called "bush surgeon from Uganda", who was in London to deliver a lecture on March 22, 1961 on "The Commonest Children's Cancer in Tropical Africa: A Hitherto unrecognized Syndrome." Dr. M.A. Epstein, who was then studying chicken tumor viruses, was led by Dr. Burkitt's suggestion of a biological cause for his tumor, to the notion that a climate-dependent arthropod vector spreading an oncogenic virus was the most likely cause of the suggested biological process.[3]

Following a trip to East Africa shortly after the eventful lecture of Denis Burkitt, Epstein was able to establish a process of supply of material from Burkitt lymphoma patients in Kampala to be flown to London. A chain of events resulting from a fog-engendered delayed delivery of one of such samples was inadvertently to result in a fortuitous observation of massive proliferation of lymphoid cells in the transit fluid. This was, indeed, the first occurrence of such an event, thus, yielding a new method of suspension culture of human lymphoid cells.[4] Over the next fifteen years, immense body of information was to be accumulated from laboratories over the world enabling the explanation of the role of Epstein Barr Virus (EBV) in endemic BL as that of "acting on a target B-lymphocyte population altered by hyperendemic malaria, an essential co-factor responsible for the climate-dependence of the tumor, to give rise either to large numbers of transformed B cells or to B cells transformed in an unusual way,[5] such that repeated cell divisions increase the likelihood of one or another of three specific chromosomal translocations[6] coming about. These translocations appear to ensure that the *c-myc* oncogene is moved from its normal site on chromosome 8 to the immediate vicinity of one of the Ig genes active in the lymphoid cell destined to give rise to the tumor,[7,8] where it would be affected by the Ig gene promoter with subsequent selection of a *myc* oncogene-driven clone of malignant BL cells".[9] The foregoing, thus, documented the earliest impression of how environmental factors became associated with a neoplastic process, and was subsequently supported with additional scientific observations.[2]

The African environment has for millennia been dominated by rampant agents of infections, of which malaria is among the best known. Other infectious agents are even postulated to be extinct.[10] The struggle between human species and the environ has led to the emergence of a variety of genetic aberrations, some of which

have been deleterious, resulting in a spectrum of diseases. One of them is the sickle cell disease, which has become recognized as a prototype of human "molecular" disease,[11] because of the factors underlying its pathogenesis. Even though it is often thought to be an "African disease," sickle cell anemia is prevalent in parts of Asia (mainly the Arabian peninsular and the Indian subcontinent), and parts of Europe (mainly Greece and Sicily), areas where historically malaria existed. Thus, the genetic disorder underlying the disease is shared by the major races of mankind: black, white and oriental.[11]

The gene for the β-chain of hemoglobin is now known to be located on the short arm of human chromosome 11.[12,13] A point of mutation in codon number 6 from GAG to GUG[14] causes glutamic acid to be replaced by valine at the corresponding 6th amino acid in the β-globin polypeptide chain[15], which entails a major physical change only in the deoxy-, but not in the oxyhemoglobin, whereby the deoxy conformation produces a unique structural feature which, eventually, leads to the process of gelling of the hemoglobin and sickling of the erythrocyte[11]. Indeed, the biological interaction between *Plasmodium (P.) falciparum* and the Hb S gene has become the most typical example in the human species of a genetic polymorphism balanced by environmental selection.[16] The mechanism of resistance to this protozoan infection has been clarified by experimental studies[17] as well as in *P. falciparum* cultures[18,19], thus, promoting the persistence of the sickle cell genetic aberration. And because of its genetic nature, sickle cell anemia is found wherever people from its geographic areas of prevalence migrate to, e.g., the Americas, Southern Nepal, and Mongolia.[11]

Examples of such functional polymorphisms include the *NOS2* and *Duffy* antigen (*DARC*) genes that evolved in Africa to resist malaria infections,[20-25] which abolishes *Duffy* expression, the erythrocyte receptor for the *Plasmodium vivax* malaria parasite[22].

The Human T-Lymphotropic Virus type 1 (HTLV-1), which is the etiological agent of Adult T cell Leukemia/lymphoma (ATL) and of Tropical Spastic Paraparesis/HTLV-1 Associated Myelopathy, was discovered in the blood of an African American man in Florida in 1979.[26] This connection to the African diaspora raised early suspicion of an African zoonotic agent. Indeed, this retrovirus, the origin of which is the STLV-1, endemic in many species of Old-World non-human primates, is present throughout the world with clusters of high endemicity located often in nearby areas where the virus is nearly absent. The main endemic areas are the Southwestern part of Japan, Sub-Saharan Africa, the Caribbeans and South America. The first case of HTLV-1 associated disease to be diagnosed on the African continent was recognized in a teenager in Ibadan, Nigeria[27].

The City of Ibadan, Nigeria, where much of the work in this report was carried out, is a unique human habitat, representing a mixture of modern lifestyle of elite professionals and academics living within short distances from poorly educated farmers and artisan workers, whose lifestyles in unplanned rural-like communities (Figure 14) hardly differs from those in nearby poorly accessible farmlands: all these within a vast area believed to be one of the largest populated urban areas in Africa.[28,29] It is also the home of one of the leading universities of Africa: the University of Ibadan, established in 1948[28,29]. The city and

its academic center, together with Kampala, Uganda, were renowned as some of the earliest centers of excellence in cancer research following the discovery of Burkitt lymphoma.[30-37] Thus, it is a unique theatre of studies of the influence of the African environment and carcinogenesis.

The purpose of this manuscript is to show that the dysparities of the clinical and laboratory features of the leukemias and the lymphomas observed in the inhabitants of Ibadan, Nigeria, as compared to those of high-income countries of Europe and North America, are the results of the prevailing environmental factors and the socioeconomic differential capacity of its inhabitants to mitigate the impact of these factors on their health.

Methods

The patients included in this study were seen and assessed clinically at the University College Hospital (UCH), Ibadan, a major medical referral center in the south-western rain-forest area of Nigeria. The Department of Hematology of the hospital was at the time of the studies described in this report was the only referral center of its kind in the region. Since the hospital attendance of the populace of the city was believed to be over 90%,[30] it was assumed that almost all cases of lymphomas and leukemias were seen and diagnosed at the hospital, and that the leukemias were registered at the Department of Hematology of the hospital, while those presenting with tumors, such as Burkitt lymphoma, were seen at the Children's Emergency Room, General Casualty Department or the Hematology Day Care Center, where initial management of very ill patients, including those with serious hematological disorders received urgent care. The inhabitants of the area were mostly peasant farmers and pretty traders, regardless of whether they lived in small villages or in large urban centres like Ibadan, which had an estimated population of between 1 and 2 million inhabitants. In view of the unavailability of census figures up to almost 20 years prior to the commencement date of the study, the population sizes of various age groups were projected from those of the last reliable census held in 1963, using various recommendations from national[38] and international bodies[39] on population changes in the area. In estimating the leukemia incidence rate (IR) for the population of Ibadan, we derived the sizes of the target population in 4 different ways: (A) by assuming a constant growth rate since 1963 at 2.5% with constant age and sex distribution: (B) by assuming a constant growth rate since 1963 at 5% with constant age and sex distribution: (C) by assuming a constant growth rate since 1963 at 2.5% with age distribution as suggested by the World Bank [1981] studies[39] and (D) by assuming a constant growth rate since 1963 at 5% and age distribution according to the World Bank studies[39]. The estimated lowest and highest incidence values are then taken to represent the range of incidence.[40]

Diagnosis of Burkitt lymphoma

The diagnosis of Burkitt lymphoma (BL) was based on clinical, cytological/histological and radiological features. This included presentation with typical jaw masses with radiological evidence of dental anarchy, and effacement of the lamina dura. Other classical clinical features included the presence of massive abdominal and or pelvic (ovarian) masses. Diagnostic

pathological features included the observation of the classical "starry sky appearance" of a hematotoxylin-eosinstained paraffin section, or the presence of cytoplasmic vacuolation of the lymphoid cytoplasm[41]. Other diagnostic methods used included bone marrow examination, lumbar puncture for cerebrospinal fluid examination, urography and ultrasonography of abdominal and pelvic structures. Routine hematologic and blood chemistry (including SGOT, SGPT, alkaline phosphatase, bilirubin, sodium, potassium, chloride, bicarbonate, uric acid) was obtained as part of initial assessment of the patients. Estimation of blood lactic dehydrogenase (LDH) was not available. Using indirect immunofluorescence technique and monoclonal antibodies[42], lymphoblasts derived from tumour sources in selected patients were immunophenotyped. Cytogenetic studies were not available.

Diagnosis of acute leukemia

Initial laboratory diagnostic tests included a complete blood count (CBC) including differential leucocyte count on a Romanovsky-stained blood film. Bone marrow aspirates were routinely obtained in all cases of acute leukaemia and lymphoma and films prepared therewith were routinely processed with May Gruenwald Giemsa stain, and, in cases of acute leukaemia, with periodic acid Schiff (PAS) and Sudan Black stains. Hematoxylin Eosin-stained tissue sections were routinely obtained for the diagnosis of malignant lymphoma. Cells for immunophenotypic characterization were obtained from the tissues involved that could be conveniently sampled. Thus, heparinized peripheral blood was obtained in the cases of acute or chronic leukemia with a total WBC in excess of $20.0x10^9$/L, while in other cases heparinized bone marrow blood was utilized. In the cases of malignant lymphoma, the samples were obtained in the forms of cerebrospinal, ascitic or pleural fluids, biopsy of enlarged lymph nodes, or the involved viscera. When necessary, such samples were teased to release an adequate quantity of cells for the procedures. The laboratory procedures of immunophenotypic characterization were performed according to the protocol of the International Study of Cell Markers in Leukaemias and Lymphomas as outlined by Greaves et al[43], using a panel of first-generation reagents including: J5[44] and AL2[45], both anti c-ALL antibody; DA 2, an anti HLA DR[46], WT 1, an anti T[47] and OKT11a, an anti E rosette receptor[48]; and My906, an anti-myeloid[49] monoclonal antibody. A number of heterologous anti sera, such as anti Ig, anti kappa, anti lambda, and anti Tdt (terminal deoxynucleotidyl transferase) were also included in the panel[50]; anti T subset murine monoclonal antibodies, including OKT3, OKT4, OKT6, and OKT8[51,52]. The binding of the monoclonal antibodies to target cells was determined by indirect immunofluorescence with fluoresceinated goat anti mouse IgG (in case of anti Tdt: rabbit anti mouse IgG) or by direct immunofluorescence in case of detection of cell-surface immunoglobulin, using a Leitz Ortholux II fluorescence microscope with incident illumination.

The capability of some T lymphocytes and B lymphocytes to form rosettes with sheep[53] and mouse red blood cells[54], respectively, was also used in the process of characterization.

Criteria for subtype characterization Of Acute lymphoblastic leukemia

Only cases of acute leukemia that did not react with the myeloid monoclonal My906

(CD33) were diagnosed as acute lymphoblatic leukemia. The subtypes of acute lymphoblatic leukemia were defined according to the previously published algorithm for the interpretation of immunophenotypic patterns observed in the International Study of Cell Markers in Leukemias and Lymphomas[42], however, with some modifications as outlined by Borowitz[55]. The subsets were defined as follows: common-ALL: CALLA+, DR+, T (WT1/E/T11)-, smIg-, Tdt+; null-ALL: CALLA-, DR+, T (WT1/E/T11)-, smIg-, Tdt-; T-ALL: CALLA+/- DR+/- T (WT1/E/T11)+, smIg-, Tdt+; B-ALL: CALLA-, DR+, Tdt-.

Gene rearrangement studies

Samples of mononuclear cells from a few of the patients stored at −80 °C for several weeks were shipped to London, England, where they were studied for the evidence of gene rearrangement using a methodology of Foroni et al.[56]

Diagnosis of HLTV infection and associated disorders

Over a period of 15 months, patients with non-Hodgkin lymphoma, Hodgkin lymphoma, Burkitt lymphoma, acute and chronic lymphocytic leukemias, consenting normal blood donors, and consenting Elementary School children were approached for blood sampling. Aliquots of 1-2 ml of sera from donated blood samples were placed in polystyrene shipment tubes and stored for 1- 6 months at -20^{0}C prior to shipment in dry ice to the Laboratory of Tumor Cell Biology of the National Cancer Institute, Bethesda, MA, USA, where they were screened for HTLV-1 antibodies by whole virus enzyme-linked immunoassay (ELISA)[57]. Confirmatory Western blot testing was performed using investigational Western blot assay incorporating the recombinant transmembrane gene product p21e into standard whole virus (Biotech, Inc)[58]. The seropositivity rates were computed as the product of the probabilities of positive outcome of the two tests. The 95% confidence intervals were computed from these characteristics using a standard statistical methodology.

Several patterns of Western blot results were identified: a multi-band pattern including strong reactivity with the gag antigen p24 and either with the external envelope gp46 and/or a recombinant p21e transmembrane portion of the envelope: an oligo banding pattern, usually p24 and gp21e; an 'indeterminate pattern' where single or multiple bands including both gag and envelope reactivity; and a negative pattern where all bands were absent. Positives included all samples with at least a gag and envelope reactivity. Indeterminants were classified as negative. These criteria of definition of reactivity pattern are similar to those suggested by the Center for Disease Control (CDC)[59] for confirming blood bank screen positive samples.

Estimating Leukemia Lymphoma Incidence

In view of lack of timely census data in the 1980s, a rough estimate of the incidence rates of human leukemias for the City of Ibadan, Nigeria had to be projected from most recent reliable census data of 1963, using various recommendations from national and international bodies on population changes in the area[38,39,60] as described earlier (see Methods).

Socioeconomic And Clustering Studies

For the purpose of studying the association of leukemia subtypes with lifestyles, the city of Ibadan[28,38,61] was sub-categorized into three

zones depending on the lifestyle and social structure of the areas:

Zone 1: the indigenous, old, and largely unplanned area, marked in Figure 13 as G for Gege, Mapo, E for Elekuro, and enclosing double lines. It was inhabited mainly by indigenes of the city, most of them were farmers, petty traders, and semi-skilled labourers. Environmental sanitation in this zone was very poor, and literacy was low. The average annual income was also very low (less than US$1,000 per year). Figures 14 shows a representative view of the quarter.

Zone 2: non-indigenous high-density area inhabited by mixed population of business people, petty traders, professionals, skilled and unskilled labourers from various parts of the country, mainly from the neighbouring Yoruba-speaking States of the Federation of Nigeria. Sections of the zone (Figures 13) include LS for Liberty Stadium, O.A. for Oke Ado, Mokola, Dugbe, S for Sabo, M for Molete.The level of education was generally higher than in the indigenous areas. The average annual income is intermediate between those of Zones 1. Figure 14 shows representative street live in the quarter.

Zone 3: low/medium population density areas, consisting largely of parkland estates and predominantly inhabited by business people, academics, and professionals. Figure 13 shows representive areas to include Agodi GRA, Moor Plantation, New GRA, Jericho GRA and B.E. for Bodija Estate. The literacy rate was high; average annual income was the highest of all the three zones, and the lifestyle was generally comparable to that of suburban Western Europe or United States. The average annual income of the inhabitants of Zone 3 areas was above $10,000 Figure 14 shows a typical street life in Bodija Estate.

Each study subject was assigned to one of five socio-economic status (SES) groups depending on the level of education and occupation:

SES Group 1: Highly educated, senior public officers, business executives (estimated annual income: $10,000 or more).

SES Group 2: Post-secondary school educated; middle-level public officers (estimated annual income: $5,000–$9,000).

SES Group 3: Post-primary school educated, lower-level public officers or institutional staff and skilled handworkers (estimated annual income: $2,000–$3,500).

SES Group 4: Primary school educated and unskilled hand-workers (estimated annual income: $1,000–$1,500).

SES Group 5: Illiterate peasant farmers and petty traders (estimated annual income: less than $1,000)

The population sizes of the various socioeconomic status (SES) groups of the residents of Ibadan city were projected from the most recently available census figures of 1963, assuming a uniform growth rate of between 2.5% and 5.0% for all five SES groups among children and adults. The distribution of the total estimated population into the various socio-economic groups was based on the studies of Odebiyi[62] and Onibokun et al.[38] The reports of these studies suggested that individuals of low-, medium-, and high- socio-economic groups in the city constituted 75%, 12.5%, and 12.5%, respectively. There was no useful information in deriving the sizes of the population of the three categories of

residential zones. Furthermore, the calculation of children and adult population within the various socio-economic groups rested on the assumption that the World Bank[39] estimation of 47% and 53% for children (aged less than 15 years) and adults (aged 15 and above) applied uniformly for all socio-economic groups. Spatial and temporal clustering of a particular disorder was determined to have taken place, respectively, if at least two cases of the disorder occurred in individuals living within a distance of 2 km of one another and within a time span of 6 months.

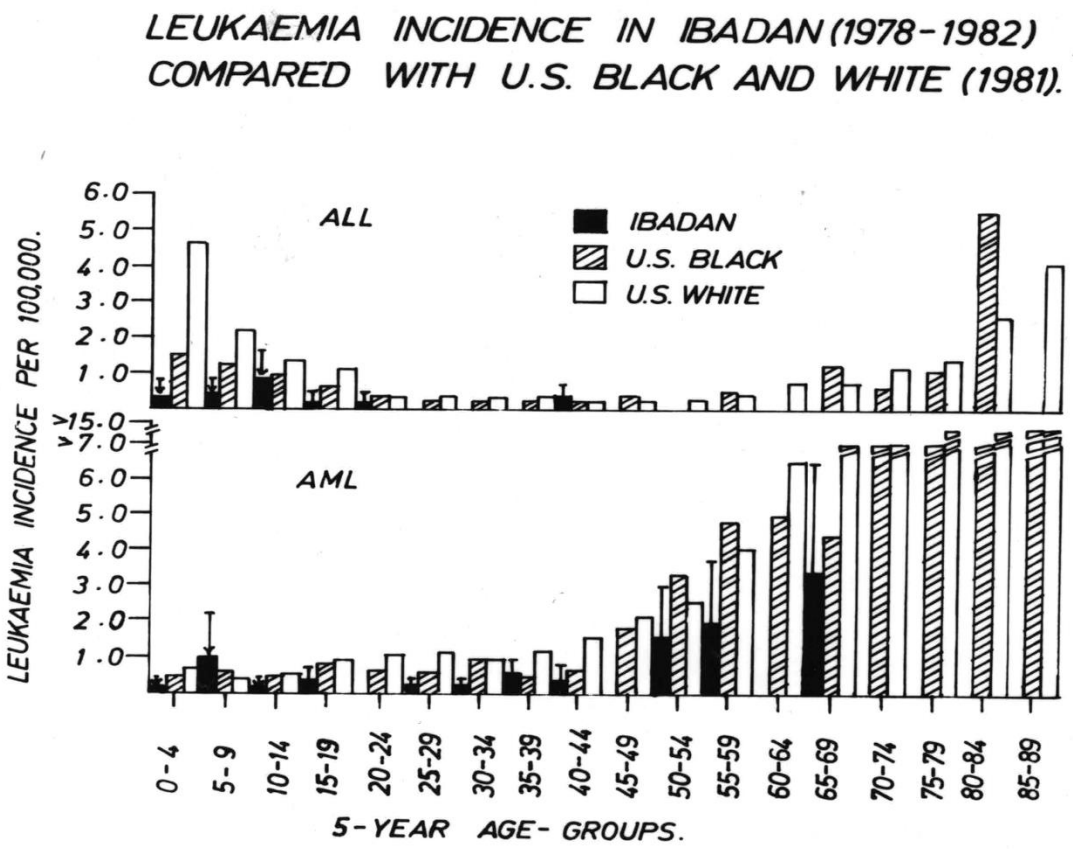
Results

Cases of leukemias and lymphomas observed at the University College Hospital, Ibadan, Nigeria between the later half of 1978 and earlier half of 1986 have previously been analysed and published with a view to shed light on some of the unique clinical and laboratory features of these diseases in a tropical locale.[27,40,61,63-94] Some of the data are again being reviewed and re-analyzed to shed light on the role of environmental and lifestyle factors on the manifestations of these diseases in the region of study and how these compare with emerging observations in other geographical populations, especially, in the African diaspora.

The leukemias

From July 1978 to June 1982 (4-year period), 33 cases of acute myelogenous leukemias (AML), 34 acute lymphoblastic leukemia, 44 of chronic myelogenous leukemia (CML), and 31 of CLL were seen prospectively at the UCH, Ibadan, Nigeria. It is believed that, applying the criteria that were used to estimate the the population sizes, criteria A and B (see Methods) appear to have considerably underestimated the population sizes of the first 3 quinquennia.[40] Thus, the lowest incidence rates of the leukemia subtypes in childhood are unknown but believed to be lower than the lower values obtained (Figures 1 and 2), hence the downpointing arrows in the histograms. The age- and sex-specific changes in leukemia incidence is bimodal with peak incidence occurring in the age as shown in Figure 3. Childhood acute leukemia in Ibadan showed a marked predilection for males. The leukemia incidence in the 20-29 years age group was low for both sexes, while the female sex predominated between 30 and 54 years. Leukemia incidence between 50 and 75 years showed a marked male predominance.

Figure 1. Incidence of acute lymphoblastic lekemia[40] and acute myeloblastic leukemia in Ibadan, Nigeria (1978-1982) compared with US Blacks and Whites. Data for US Blacks and Whites were obtained from SEERS.[95]



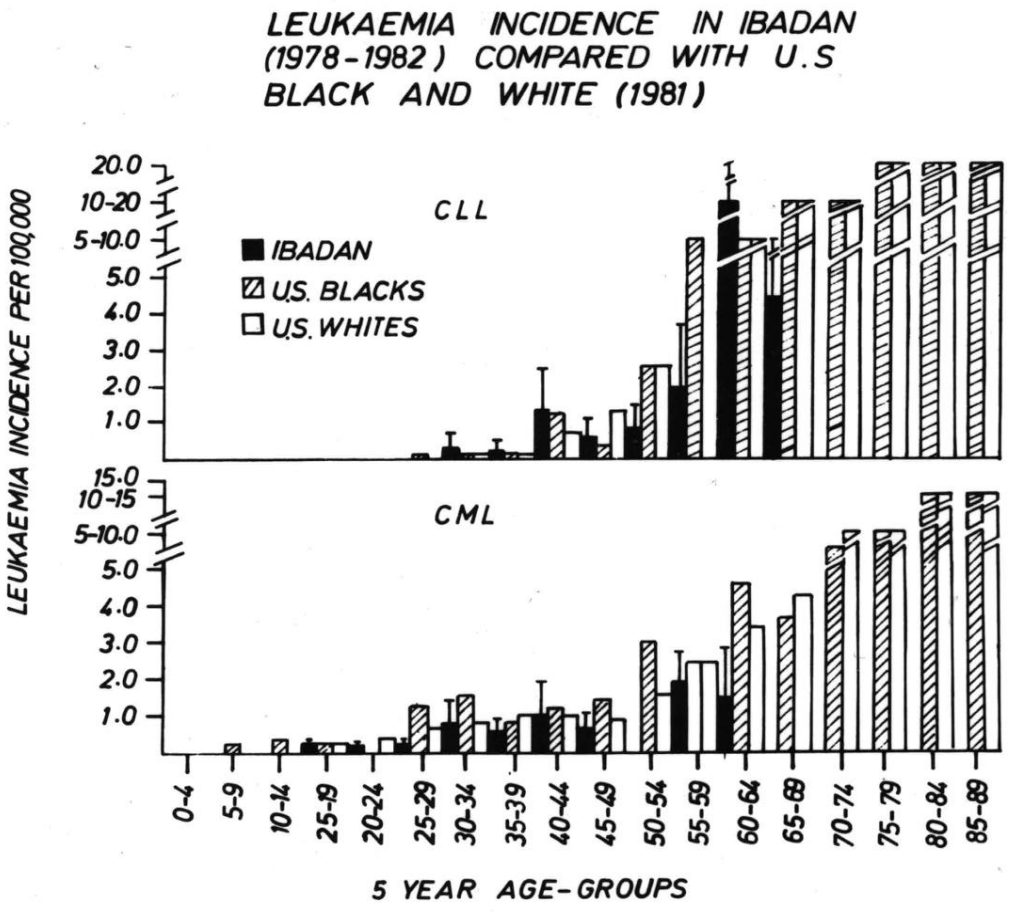
The age- and sex-specific incidence of all leukemia subtypes observed in Ibadan in 1978-1982 shown in Figure 3 reflects the marked prevalence of acute myeloid leukemia and acute lymphoblatic leukemia in boys as shown by male:female ratios of 7:1 and 3:1 respectively for acute leukemia cases occurring below the age of 14 years. The large female excess in leukemia incidence between the ages of 30 and 49 years is largely due to the larger number of cases of CLL, with male:female ratio of 1:6, while the male excess in leukemia incidence after age 50 is due to the higher prevalence of CLL in men as shown by the male:female ratio of 2:1.[40]

The availability of incidence data for Ibadan residents, even though only in crude estimates, has enabled a comparison with leukemia rates in other geographic climes and populations.[40] This is particularly relevant to the United States (US), with its population diversity, including its inhabitans of African descent, as well as the excellent cancer data bank in form of the Surveillance, Epidemiology and End Results (SEER) Program.[95,96] Figure 1 and Figure 2 show a comparison of leukemia incidence rates in Ibadan in this study with those of contemporaneous African (Black) and Caucasian (White) American populations. In all three populations, the incidence of acute leukemia was bimodal, being highest is childhood and old age. The most striking differences are observed in the first and second quinquennia, whereby acute

lymphoblatic leukemia incidence rate in Caucasian (White) Americans and African (Black) Americans are at least 5- and 2.5-fold respectively higher than in Ibadan children, while in the second quiquennium, the acute myeloid leukemia incidence rate in Ibadan is highest of acute lymphoblatic leukemia three populations. The acute lymphoblatic leukemia incidence in the second quinquennium in US Caucasian (White) children is at least twice as high as in Ibadan children. All incidence rates appear to be similar for all three population groups in the third quinquennium. The peak incidence of acute myeloid leukemia in Ibadan children in the second quinquennium is probably related to the frequent occurrence of chloroma-associated variant of the disease (choroma-associated acute myeloid leukemia), which afflicts boys of this age group (see Figure 4 and Figure 9 – right panel).

The incidence of CML was similar in all three populations, except that the disease was not recorded in the Ibadan population after the age of 64, unlike the observations in CLL, in which peak incidence occurred in the age-groups 40-44 and 60-64 in Ibadan patients, different as compared to the American rates. The remainder of the observations beyond age 69 is probably due to survival differences.

Figure 2. Incidence of chronic lymphocytic (CLL)[40] and chronic myelocytic leukemia (CML) in Ibadan (1978-1982) compared with US Blacks and Whites. Data for US Blacks and Whites were derived from SEERS.[95]



International Comparative Studies

Further to the comparison of the estimated leukemia incidence patterns between Ibadan patients and those of the African (Black) and Caucasian (White) populations of the US, previously outlined in Figure 1 and Figure 2, the pattern of the incidence of all immunophenotypes of these three populations[81,97-101] is extended to include those of the United Kingdom (Figure 5). Although the incidence of acute lymphoblatic leukemia among Nigerian children was estimated to be less than a third of those of the Caucasian children of the UK and the US, and just over 60% of that of African American children, yet the incidence of T-ALL was not remarkably different in the four groups of children, ranging between an estimated 0.31 x 10^{-5} value for Nigerian children through 0.35 x 10^{-5} and 0.38 x 10^{-5} respectively, for the UK and Caucasian and African Americans respectively. Thus, the incidence of the T-ALL subtype served as an internal control, indicating that the reduced incidence of other acute lymphoblatic leukemia subtypes was unlikely to be due to underdiagnosis. The incidence of c-ALL in the presumed Caucasian UK and Caucasian American children, however, at 1.83 and 1.91 respectively, was at least ten-fold, and that of African American children, estimated at 0.70, almost three times higher than that of Nigerian children, which has been estimated at 0.18. The incidence of B-ALL among Nigerian children, estimated at 0.18 is three to nine times higher than that of among Caucasian American and UK children with rates of 0.06 and 0.02, respectively. Thus, the main differences in the incidence of acute lymphoblastic leukemia in the four populations is principally attributable to the differences in the incidence of non-T-ALL, which in essence references the c-ALL subtype.

Figure 3. Age- and sex-specific incidence of acute lymphoblatic leukemia subtypes of leukemia in Ibadan (1978-1982).[40]

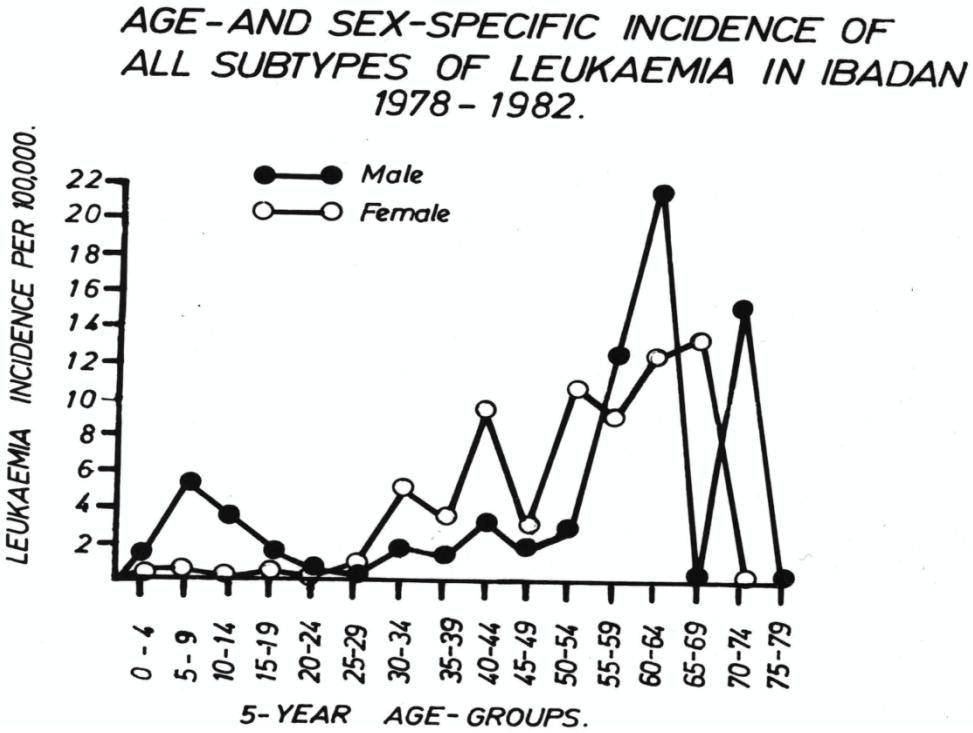
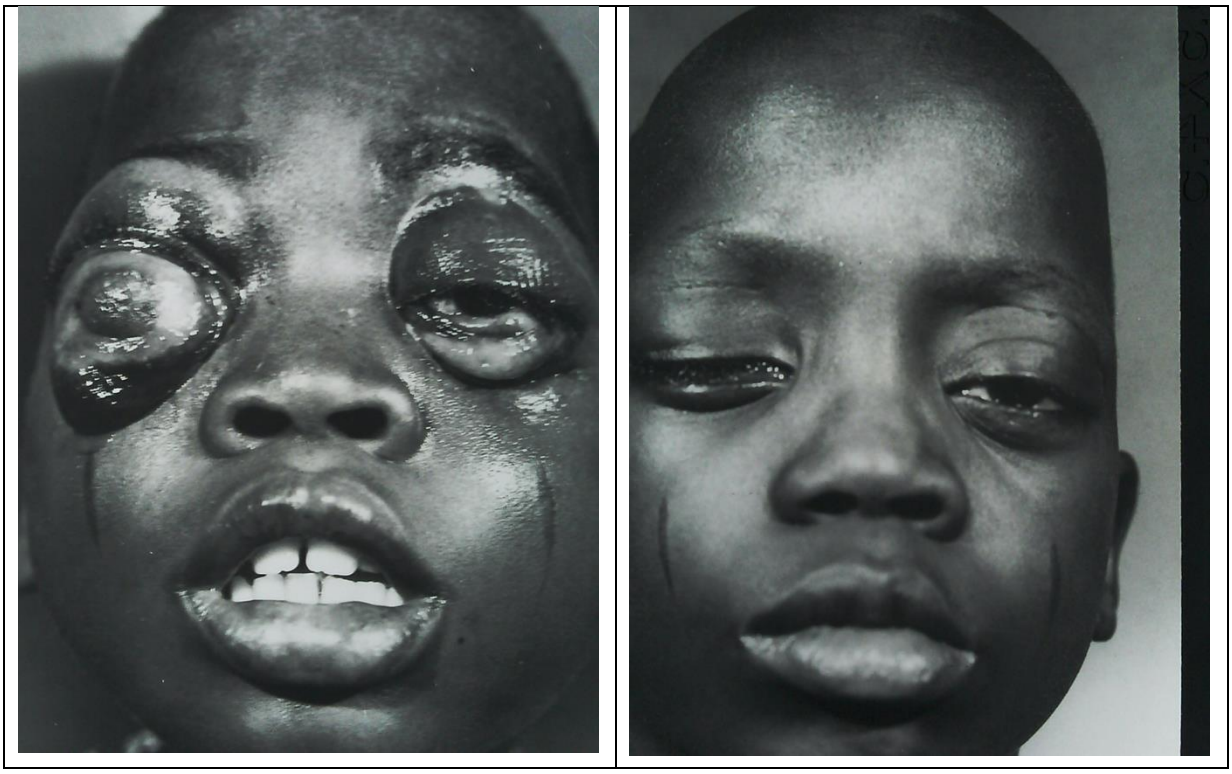


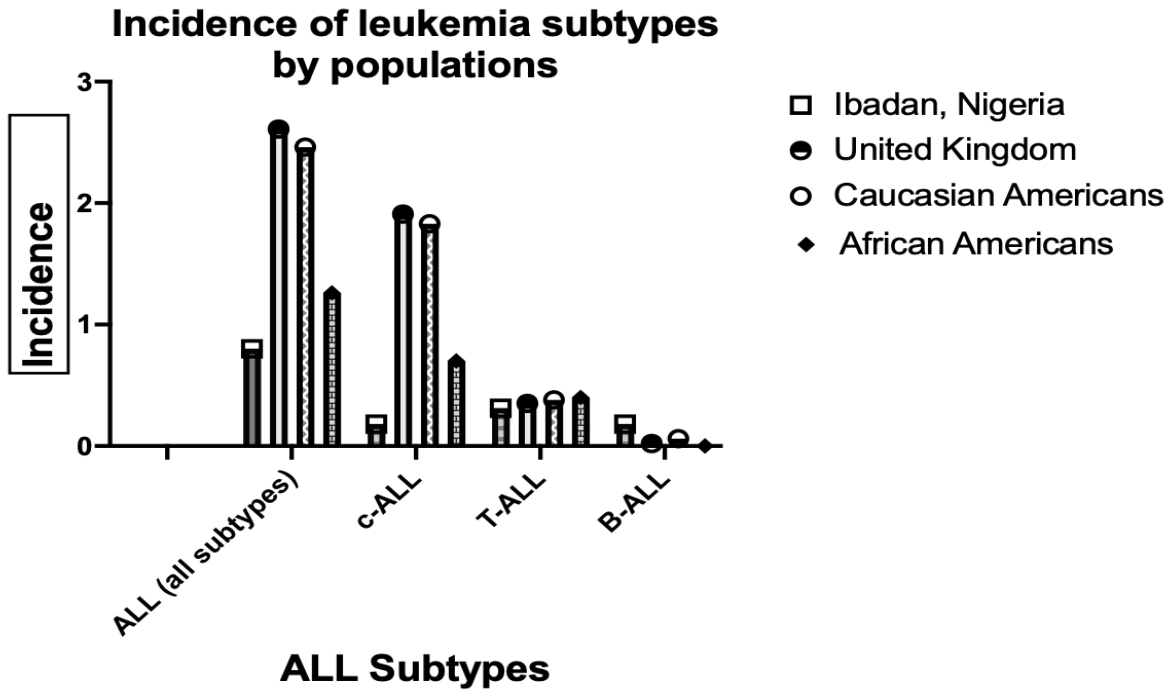
Figure 4. Nine-year old Nigerian boy with acute myelogenous leukemia associated with bilateral orbital chloroma. Left before, and right after chemotherapy.



A correlation of the incidence of leukemia and lymphoma, based on immunophenotypic[43,49,100] and/or gene rearrangement[56,80,102] analyzes with the socioeconomic status of the patients (see Methods) aged <15 years and >15 years are shown in Figure 7 and Figure 8, respectively. In both age-range categories, there is a significant correlation between disease incidence and socioeconomic status (p=0.0024 and p=0.0043, respectively). A number of features appear to be striking in the correlations between the disease incidence and SES, including the following:

a. among children (age <15 years – Figure 7), low SES is strongly correlated with BL and acute myeloid leukemia (presumably the choroma-associated variant); b. acute lymphoblastic leukemia and HD are strongly associated with rising SES; c. in Figure 8, the incidence of CML, which is globally recognized as "molecular disease" due to its unique linkage to the BCR/ABL gene rearrangement as well as the Philadelphia chromosome, shows no SES disparity. However, there is a correlation in CLL with low SES, also confirmed in Table 1, which shows clustering of CLL cases in zone 1; d. the pattern of incidence linkage with SES in HD, with its complex subtypes,[103,104] would seem to suggest a complex association with the SES of Nigerians.

Figure 5. Incidence of leukemia subtypes by country: Ibadan,[81] United Kingdom,[100] Caucasian America[97] and African American.[97]

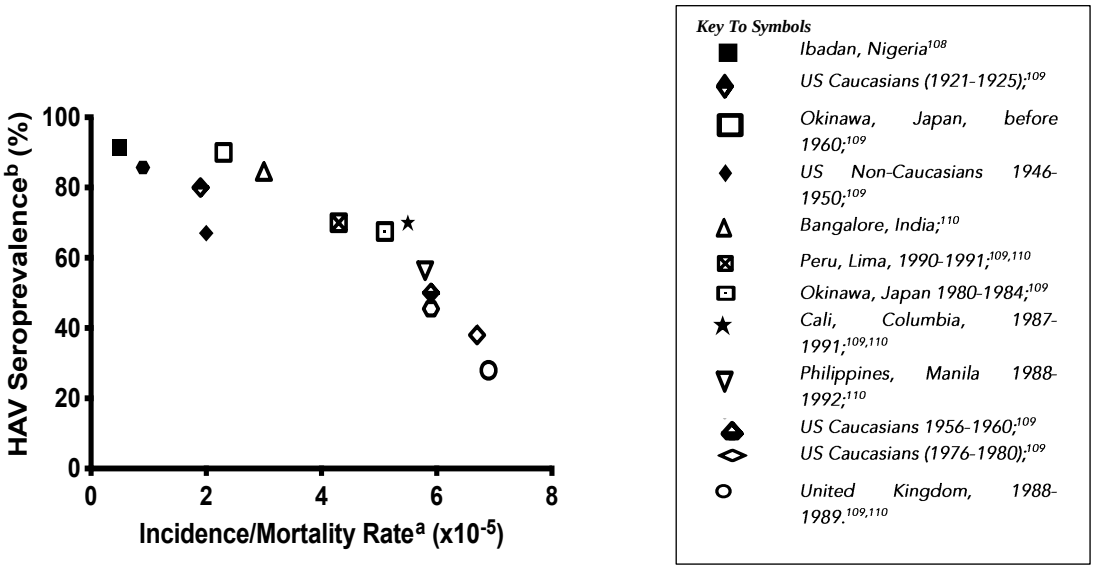


Discussion

The basis of oncologic anthropology

Denis Burkitt's discovery in 1958 of the disease that bears his name[1] and its linkage to the African environment was not only a landmark in the history of cancer research, it was a watershed in the recognition of the role of microbials, including bacteria, viruses and parasites,[2] in carcinogenesis. There are several examples of genetic polymorphisms that are frequent in populations of African descent, which have emerged due to their effect in resistance to parasitic infections, but may increase susceptibility to other diseases including cancer[105]. Examples of such functional polymorphisms include the *NOS2* and *Duffy* antigen (*DARC*) genes that evolved in Africa to resist malaria infections,[20-25] by abolishing *Duffy* expression, the erythrocyte receptor for the *Plasmodium vivax* malaria parasite[22]. The importance of some of these polymorphisms in addressing cancer disparities in multi-ethnic populations, for instance, in relation to TNBC has been well documented,[106] and has led to the coining of the expression "oncologic anthropology",[107] but their role in hematological neoplasias are less certain.

Figure 6: Indices of public hygiene, e.g., HAV seroprevalence, infant mortality, and incidence/ mortality of ALL in eight countries at different stages of development



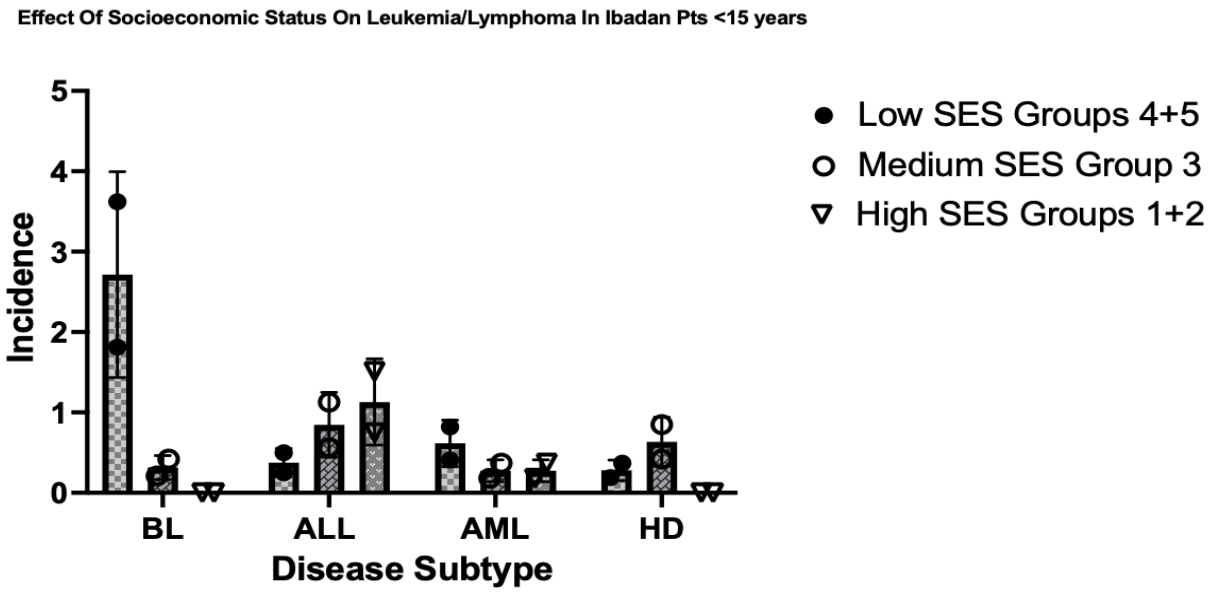
Enviromental Factors in The Leukemia/ Lymphoma of African Children

From the numerous publications describing the biological and epidemiological features of the leukemias in Africa,[40,61,71,74,81,82,85,111-127] a number of unique features of this group of diseases have been recognized. A comparison of the incidence rates for acute leukemia in Ibadan and in African American and Caucasian Americans is shown in Figure 1. The most striking differences occurred in the first quinquennium in which acute lymphoblatic leukemia was, at least, 10 times as common in Caucasian, and at least twice as common in African American children as in Ibadan children. Acute myeloid leukemia, however, was at least twice as common in Ibadan children as in the African American and Caucasian American children, with the peak incidence of the disease occurring in the 2nd quinquennium in Ibadan children. The most striking clinical feature chacteristic of acute myeloid leukemia in parts of Africa is its frequent association, especially in childhood, with chloromas[81,113,128] (Figure 4). This form of presentation of acute myeloid leukemia is not unique to Africa. It used to be more frequently observed in various parts of parts of Europe,[127,129] although it has been estimated to occur about 30 times more frequently in Ibadan than in British children.[81] It has also been reported from Turkey[130], and other parts of the world.[131,132] Apart from the impression of late disease manifestation, chloroma-associated acute myeloid leukemia in Ibadan has specific epidemiological features, including prominence in the second quinquennium (5 of 9, 55.6% children) (Figure 9), with involvement of various parts of the body, e.g., central nervous system, the vulva, the palate and the soft-tissue of the respiratory system.[93,128]

The role of environtal factors in carcinogenesis is probably best appreciated in the studies of cancer patterns in early life. Such studies conducted in developed countries seem to

emphasize the role of "manufactured" or "engineered" environments, such as exposures to ionizing radiation[133-136], chemical exposures, such as human carcinogens[137]. Despite the dramatic advances attained in the management of acute lymphoblastic leukemia over the last six decades[138], the cause of the disease remains unknown. The epidemiology of the disease has, however, evolved since the early 1900s and in different parts of the world, beginning in the period of 1921 to 1929 in the United Kingdom,[42] and later documented in the United States[139] with the earliest observation of a peak incidence of the disease between the age of 1 and 5 years. Such an observation had, however, not been made in Sub Sahara Africa even up to the mid-1980s. This observation would tend to suggest a link to socioeconomic conditions and concomitant exposure to potential leukemogenic agents.[42]

Figure 7. Correlation of the incidence of Burkitt lymphoma, acute lymphoblastic leukemia, acute myelogenous leukemia and Hodgkin lymphoma in Ibadan children (age: <15 years) with SES: See Methods, and Williams 2014.[80]



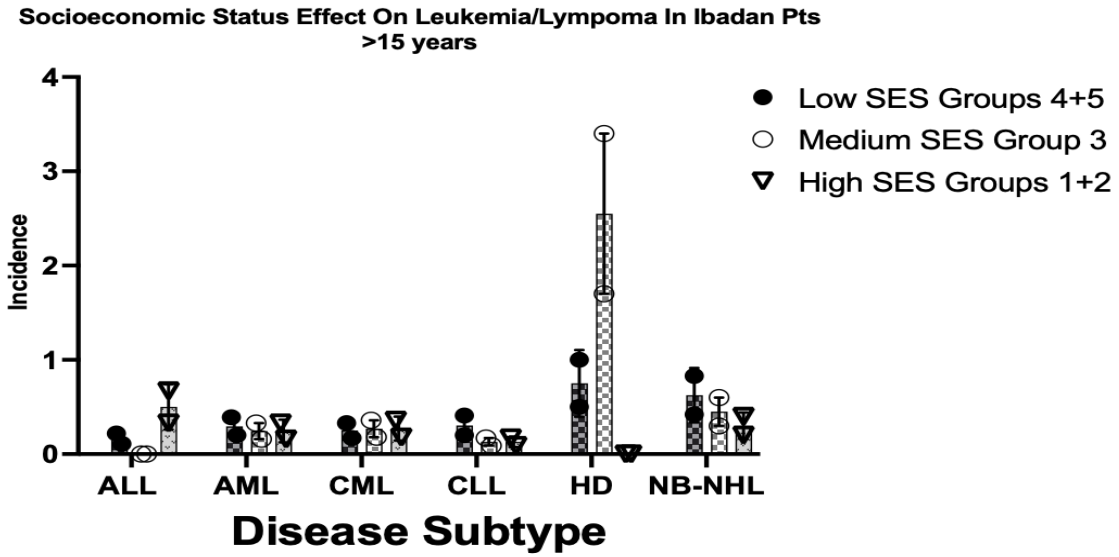
Ludwig Gross Experiments - The Hypothesis of Thymolymphatic Deficiency

The idea that acute lymphoblatic leukemia is a disease associated with improved living standards has gradually gained credance,[42,139-141] with Ramot and Magrath being first in proposing such a specific hypothesis for observations of acute lymphoblatic leukemia among Arab children living in the Gaza Strip.[142] The differences between the biological and epidemiological features of leukemia in Africa and the developed societies of Europe and the US, as described earlier, cannot be explained by genetic differences but rather by the marked differences in lifestyle and socioeconomic situations. The pervasive poverty of the African people leaves them completely unprotected from the vagaries of the natural environment and and the consequencies of economic deprivation, including malnutrition, parasitic and other opportunistic infections and poor sanitation. Thus, it is pertinent to consider the role of infection and hygiene in the community in

leukemia etiology. Figure 6 illustrates a correlation of the global incidence of childhood acute lymphoblastic leukemia with index of hygiene, e.g., hepatitis A virus (HAV) seroprevalence in the first decade of life, or infant mortality rate.[143] The latter has been used as a surrogate index of HAV seroprevalence rate.[109] This association, which was first advanced by Smith et al[109] has been extended to describe the acute leukemia incidence in eight nations, some at various times of their socioeconomic development. The correlation (Pearson) is highly significant (p value = <0.0001).

Studies in both experimental animals and humans have established that severe atrophic changes of the thymolymphatic system are a constant feature in malnutrion, and that these changes are most pronounced and least reversible when they occur during the intrauterine period or very early in infancy. The mechanism underlying these changes is believed to be related to the increased uptake of free circulating adrenocorticosteroids as well as to a deficiency of certain nutrients required for the development of the thymolymphatic system. Consequently, there is a depletion of circulating T-lymphocytes, and this manifests in form of an impartment of cell-mediated immunity and increased susceptibility to infection.[144-146]

Figure 8. Correlation of the incidence of Burkitt lymphoma, acute lymphoblastic leukemia, acute myelogenous leukemia and Hodgkin lymphoma in Ibadan patients aged >15 years, with their SES (see Methods, and Williams 2014.[80])



The unique features of acute leukemia described in Ibadan children, as described earlier, including the reduced incidence of acute lymphoblatic leukemia in the first quinquennium and the increased incidence of acute myeloid leukemia, especially in the 2nd quinquennium, often in association with chloromas, are reminiscent of the observations of Gross[147] on the influence of environmental factors in leukemogenesis. Following underfeeding of Ak mice, Gross observed a delay in the onset and in the rate of occurrence of virus-induced and spontaneously occurring leukemia. Although spelenectomy of C3H mice did not alter the incidence or latency of virus-induced leukemia, thymectomy inhibited or considerably delayed

the development of lymphatic leukemia, and frequently caused the myelogenous forms to appear later in life, often in the form of "chloroleukemia." The pattern of leukemia in African children may thus be Nature's equivalent of Gross's observations. The mechanism of this phenomenon, which is illustrated in Figure 11, appears to affect most profoundly, if not selectively, the development of the c-ALL variant.[87]

Table 1

Occurences of clustering[72] of cases of hematological malignancies in areas of Ibadan, Nigeria, 1978-1983 (see Figure 13)

	Zone 1	Zone 2	Zone 3	Total
	N (%)	N (%)	N (%)	
BL[a]	13(92.9)	1(7.1)	0	14
ALL[b]	0	2(66.7)	1(33.3)	3
AML[c]	4	0	0	4
CML	0	0	0	0
CLL[d]	4(100.0)	0	0	4
HD[e]	3(50.0)	3(50.0)	0	6
NB/NHL[f]	4(100.0)	0	0	4
Total	28(80.0)	6(17.7)	1(2.9)	35

a= 14 in 31 patients; b= 3 in 6 patients; c= 4 in 8 patients. CML: 0; d= 4 in 9 patients; e= 6 in 12 patients; f: 4 in 10 patients.

Environmental Factors and Chronic Leukemia Subtypes in Nigerians

A comparison of the incidence of CLL and CML in the three populations is shown in Figure 2. The only striking differences are observed in CLL in 40-44, and 60-64 among Ibadan patients. There are no striking differences among the three populations in CML. Figure 3 further clarifies the male predominance in leukemia incidence to be ascribable to chloroma-associated AML, CLL among women in the 40-44 age-group, and men with CLL in the 60-64 age-group. The female excess observed in some African countries among CLL patients below the age of 50 years led to the suggestion that this might be due to pregnancy-associated immune-suppression and the additive influence of an oncogenic virus, which was speculated to be HTLV-1.[127,148] Two of 20 (10%) of CLL, but none of 8 cases CML, tested seropositive for HTLV-1 (Table 2) in this study. Given the high rate of seropositivity in healthy blood donors in this population, the role of HTLV-1 infection in the etiology of this immunodeficiency related hemopoietic disorder is unclear.[87] It has, however, been suggested that there might be two forms of CLL in Nigeria: an "endemic variant," which occurs frequently below the age of 50 years among women, and a "non-endemic form" occurring in older individuals. The former CLL variant is probably related to immune-deficiency state occurring consequent to the lifestyle of low socioeconomic status (Figure 8, Table 1).

Table 2

Pattern Of HTLV-I Results in Normal Individuals and Patients with Neoplastic and Non-Neoplastic Disorders in Ibadan, Nigeria, 1984-1985

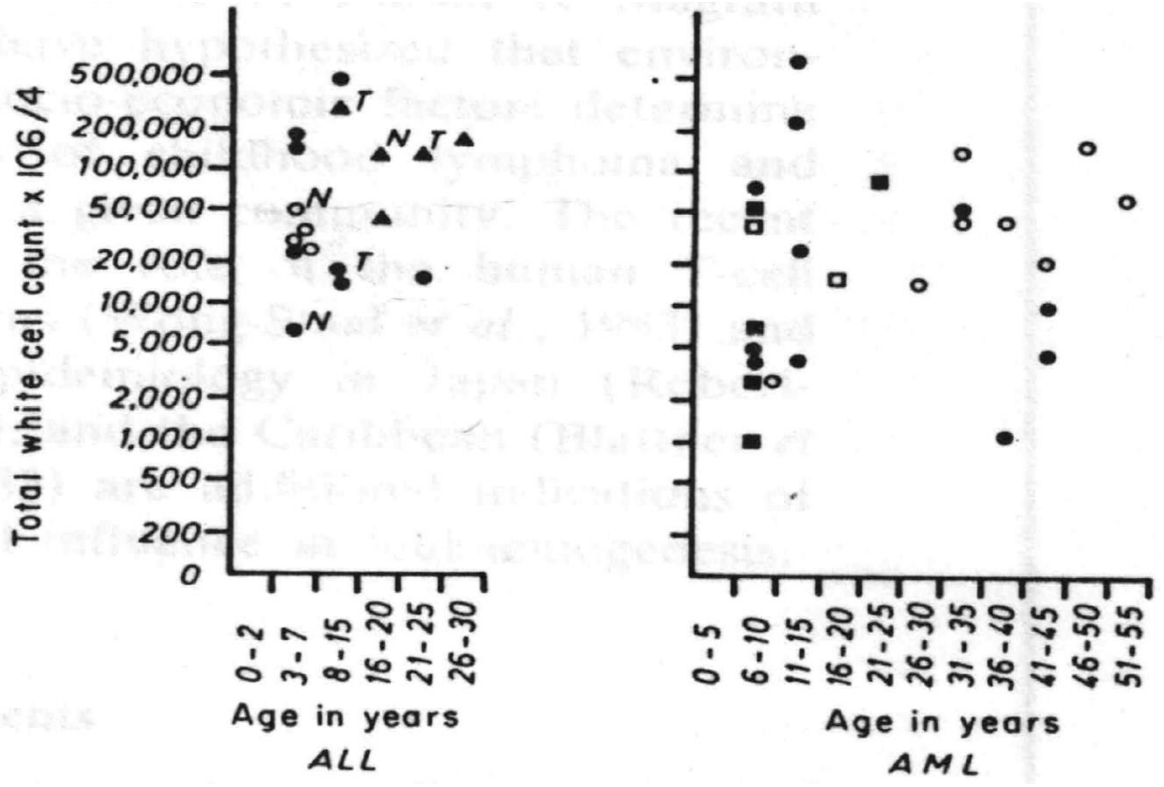
	Western Blot Determined Status					
WB Status	Negative	Indeterminate	Positive	Not done	Total# studied	%Seropositivity
Lymphoma						
ATL	0	0	4	0	4	100.0
Non-ATL						
NB/NHL	9	9	2	7	26	10.5
BL	8	8	7	1	47	14.4
HD	3	3	0	0	13	0.0
Leukemias						
ALL	7	0	3	4	26	13.6
CLL	4	1	2	1	21	10.0
CML	4	1	0	1	9	0.0
Other cancers	6	3	2	6	28	9.1
Non-cancer Chronic disorders	11	1	3	7	33	11.5
Normal						
Blood donors	29	16	9	27	123	9.3
School children	3	1	3	25	46	14.2
Total no. studied	84	34	39	79	380	12.9

Sickle Cell Disease and Leukemia Epidemiology

Following recent improved survival of sickle cell disease patients, attention is now turning to their risk for non-communicable diseases. A recent study showed that compared with the general California population, sickle cell disease patients had a 72% increased risk of hematologic malignancies and a 38% reduced risk of solid tumors. Sickle cell disease patients were not at increased risk for most cancer types, with the exception of leukemia where sickle cell disease patients had over a twofold increased risk. Among subtypes of leukemia, the risk was higher for acute myeloid leukemia (SIR, 3.59; 95% CI, 1.32-7.82) and borderline

increased for chronic lymphocytic leukemia (SIR, 4.83; 95% CI, 1.00-14.11).[149,150] Our study of leukemia patients in Ibadan reported here did not address their sickle cell genotype or phenotype. However, given the high likelihood that the sickle cell disease patients were African Americans, it seems reasonable to assume that the California data have some bearings on acute myeloid leukemia etiology in the people of African descent, hence prompting the relevance of acute myeloid leukemia epidemiology in the global population in general and the people of African descent in particular. Based on a recent World Health Organization (WHO) publication, the global

Figure 9. White cell counts and the presence of solid tumors at diagnosis. Closed circles = males, open circles = females; closed triangles = acute lymphoblatic leukemia males with tissue invasion (e.g., mediastinal and testicular masses; closed rectangles = AML in males with chloromas; open rectangles = AML in females with chloromas; T = T-cell ALL; N = Null-cell acute lymphoblatic leukemia.[93]



AML/ALL ratio is 2.19.[151] This value is similar to the AML/ALL ratio ranging from 0.7 to 2.2 obtained from several African centers between 1958 and 1976 (Table 3). However, given the dysparaties of global exposures to leukemia causing agents, including tobacco,[152] childhood AML/ALL ratios are, probably, more likely to provide more useful information in connection with etiologic discovery. These values are provided in Table 4. Since the occurrence of Wilms's tumor is said to vary little throughout the world,[125,153] the AML/Wilm's Tumor ratio may also be a useful index. This is 0.59 in Ibadan, and 0.61 in African American, compared to 0.54, and 0.97 in Swedes, and Caucasian Americans, respectively, thus, signifying etiological genetic ancestry-related dysparities between the former and for the latter group.

Figure 12 shows a comparison of childhood AML/ALL incidence/frequency rate ratios between people of African descent and those of Caucasian descent. The differences are assessed as statistically significant (p= 0.0302). Comparable data set for adults is, however, not available. One possible interpretation of this observation is that people of African descent are geneticacally more prone to develop acute myeloid leukemia than Caucasians are.

Is There a Link Between Duffy-Associated Neutropenia and Leukemogenesis?

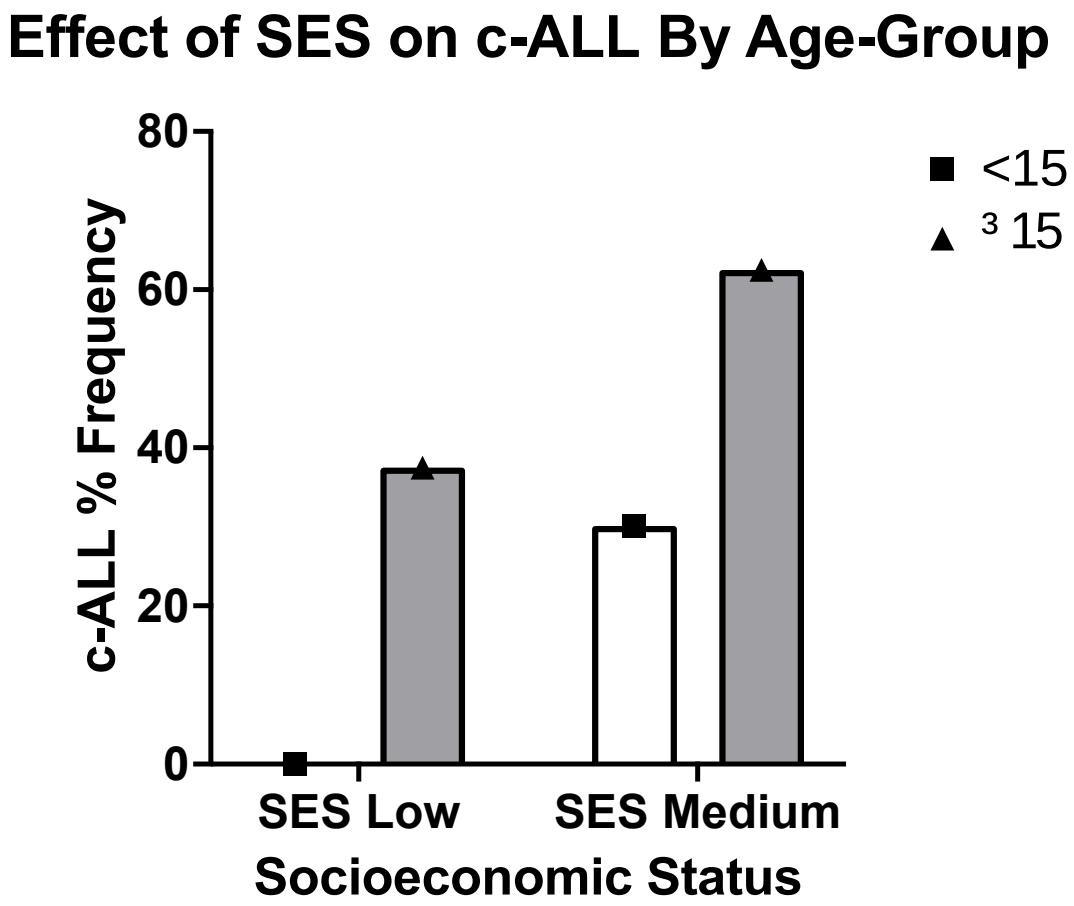
It would seem that some factors related to sickle cell disease play a role in the pathogenesis of acute myeloid leukemia, but less so in acute lymphoblastic leukemia. The dysparities could be some genetic ancestral factors that sickle cell disease patients probably share. One such factor could be the Duffy-null allele, which are linked with the commonly observed laboratory abnormality of asymptomatic neutropenia in people of African descent. This used to be known as "ethnic neutropenia," but was recently re-named "*Duffy*-associated neutropenia"[154]. While this is a benign condition,[155] it would seem reasonable to speculate that the ancestral genetic defect, which causes the Duffy-associated neutropenia, probably, also plays a role at some stages of granulopoiesis and myeloid leukemogenesis in Ibadan, Nigeria, and Africans in general, as well as in people of African descent.

Lifestyle and Cancer Subtypes

Socioeconomic status (SES), defined by income and level of education, has been associated with cancer mortality as well as estrogen receptor (ER) status of breast cancer. It has been established that populations with a low socioeconomic status are more likely to develop an ER-negative status than populations with a high socioeconomic status[156-159]. In terms of observations in geographical populations, a study of 507 breast cancer patients from West Africa revealed that 55% had a triple-negative disease which is significantly a higher proportion than one would expect to find in the same age cohorts of African-American, European-American or European patients[160]. Assuming that it is logical to characterize West African locality as being of lower socioeconomic status as compared to American or European localities, the observation among the West African breast cancer cohort would seem to be consistent with the earlier observation linking lower socioeconomic status with the higher frequency of ER-negative breast cancer. Nonetheless, it has been reported that "ER status seems to fall short of explaining most of the observed differences in tumor ER status between women of African and European ancestry"[105]. The importance of polymorphisms in addressing the question of cancer disparity in multi-ethnic populations has recently been addressed in a study of a cohort of 2884 breast cancer cases including 760 African American, 962 Caucasian American, 910 West African/Ghanaian, and 252 East African/Ethiopians, who were analyzed for genotypes of candidate allees. A subset of 417 healthy controls were also genotyped, to measure the associations with overall breast cancer risk and triple negative breast cancer (TNBC). TNBC frequency was highest in Ghanaian and African American cases (49% and 44% respectively; $P < 0.0001$) and lowest in Ethiopean and Caucasian American cases (17% and 24% respectively; $P < 0.0001$). TNBC

cases had higher West African ancestry than non-TNBC ($P < 0.0001$). Frequency of the *Duffy-null* allele (rs2814778: an African ancestral variant adopted under selective pressure as protection against malaria) was associated with TNBC-specific risk ($P < 0.0001$), quantified West African Ancestry ($P < 0.0001$) and was more common in African American, Ghanaian, and TNBC cases. Thus, West African ancestry is strongly correlated with TNBC status, and the *Duffy-null* allele was associated with TNBC risk in this cohort.[106]

Figure 10: Analysis of SES vs c-ALL subtype by age-group.

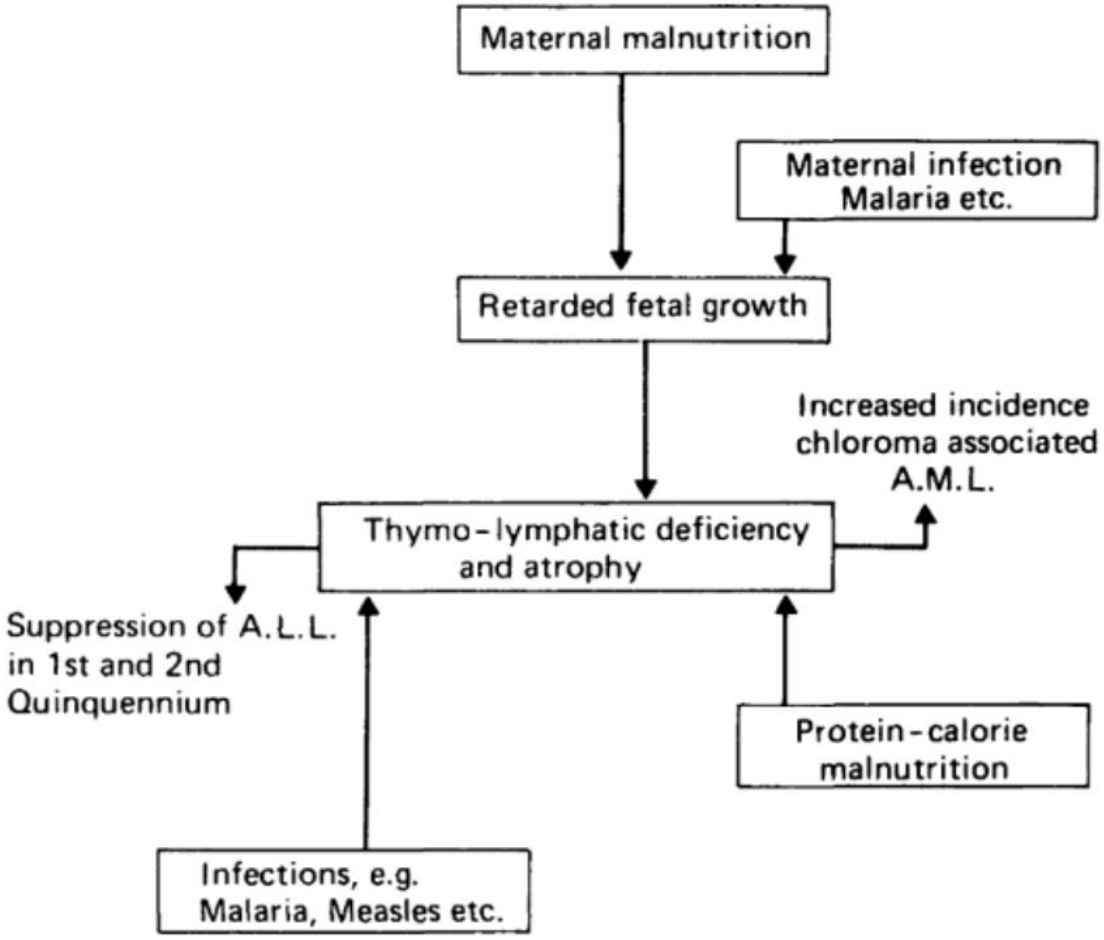


The linkage of low socioeconomic status with ER-negative breast cancer is comparable to the linkage of low socioeconomic status to high incidence of Burkitt lymphoma and chloroma associated acute myeloid leukemia (Figure 4 and Figure 7) in Ibadan patients under 15 years of age. On the other hand, the association of higher socioeconomic status with ER-positive status in breast cancer is less clear.[161,162] Generally, more affluent populations have a higher risk of breast cancer and increased prevalence of ER-positive tumors,[156,163] with some variations across race/ethnic stata.[105,164]

Figure 5 shows that c-ALL subtype is a disease of high-income populations of the UK and USA. Figures 7 and 8 show that it is only the incidence of acute lymphoblastic leukemia that increased with increased socioeconomic status both in chidren (i.e., <15 years) and patients above 15 years, thus, indicating that increased socioeconomic status in Ibadan is

likely to lead to increased incidence of c-ALL. The analysis of socioeconomic status vs c-ALL subtype by age-group, shown in Figure 10, confirms that a change of socioeconomic status from low (average annual income of less than US$ 1,000) to medium ($ 2,000 - $ 3,500) is significantly associated with an increase in the frequency of c-ALL from 0/6 (0%) to 2/6 (30%) in the <15-year age-group, and from 3/8 (37.5%) to 5/8 (62.5%) in the ≥15-year age group (p= 0.0464).

Figure 11: A proposed hypothesis to explain some of the epidemiological features of childhood acute leukemia in Nigerians.[87]



HTLV-1 In Health and Disease

All four cases of non-Burkitt NHL (NB/NHL) with clinical features of ATL[165-167] featured in Table 2 were HTLV-1 positive and were therefore diagnosed as cases of adult T-cell leukemia/ lymphoma (ATL), the sentinel disease of HTLV-1. Two of other 19 tested NB/NHL cases, which lacked the clinical features of ATL, but tested seropositive for HTLV-1, could not be identified as ATL cases. Thus, only 4 of 23 (17.3%) tested NB/NHL cases studied in Ibadan in the 1980s had features of ATL. This frequency rate of the disease in a major endemic area of HTLV-1 infection in Africa was low in comparison to the 50% to 60% rates of other major endemic areas of Jamaica and Japan.[68,168-170] As has

previously been pointed out, this relatively low frequency rate could be attributed to either an increased frequency of non-ATL NB/NHL or a reduced prevalence of ATL in the study population of Ibadan.[84] The HTLV-1 seroposivity rates for other disease types range between 0% (CML and HD) and 14.4% in BL. However, given the seropositivity rates of 9.3% in blood donors and 14.2% in school children, it is difficult to link any disease entity in this locale, with HTLV-1 infection, apart from ATL.

Table 3

Acute Leukemia in Africa – 1958 - 1982

Regions	Countries[Ref]	Study period	Total #		% with chloroma	AML/ALL ratio
Central Africa			AML	ALL		
	Democratic Republic of the Congo[114]	1958-1963	7	?10	14	0.7
East Africa						
	Kenya[118]	1967-1969	12	6	N/A	2.0
	Uganda[117]	1965-1966	N/A	N/A	11	N/A
Southern Africa						
	Harare, Zimbabwe[115]	1959-1964	?10	?5	N/A	?2.0
	Harare, Zimbabwe[122]	1967-1969	10	11	0	1.1
	Harare, Zimbabwe[124]	1967-1972	21	25	N/A	.84
West Africa						
	Ibadan, Nigeria[112]	1958-1962	N/A	N/A	N/A	N/A
	Ibadan, Nigeria[121]	1958-1968	57	26	3.5	2.2
	Zaria/Kaduna, Nigeria[127]	1970-1976	28	21	N/A	1.3

Ref: Reference; N/A: Not available.

Table 4[a]

Some Features of Childhood Acute Leukemias in Ibadan, Nigeria, Contrasted with Those of the United Kingdom, the United States and Sweden. A Comparison of The Influence of Ancestry On AML/ALL Incidence/Frequency Ratios

	Africa	Europe		USA	
	Ibadan, Nigeria	United Kingdom	Sweden	Caucasian Americans	African Americans
Study period[ref]	1978-1981[81]	1954-1977[98]	1958-1974[171]	1973-1982[99]	
ALL					
Incidence (x 10^{-5})	0.8	2.61	N/A	2.46	1.29
ALL/Wilm's Tumor Incidence Rate	1.1	N/A	3.73	3.27	1.67
AML					
Incidence (x 10^{-5})	0.8	0.5	N/A	0.74	0.47
AML/Wilm's Tumor Incidence Rate	0.59	N/A	0.54	0.97	0.61
AML-WT/ALL-WT Incidence Ratio	0.53	N/A	0.14	0.29	0.36
AML/ALL Incidence Rate Ratio	1.0	0.19	N/A	0.39	0.47
AML/ALL Rel. Freq. Rate Ratio	0.52	0.25	0.17	0.3	0.37

ref: references; N/A: Not available; a: adapted from Williams et al.[81]

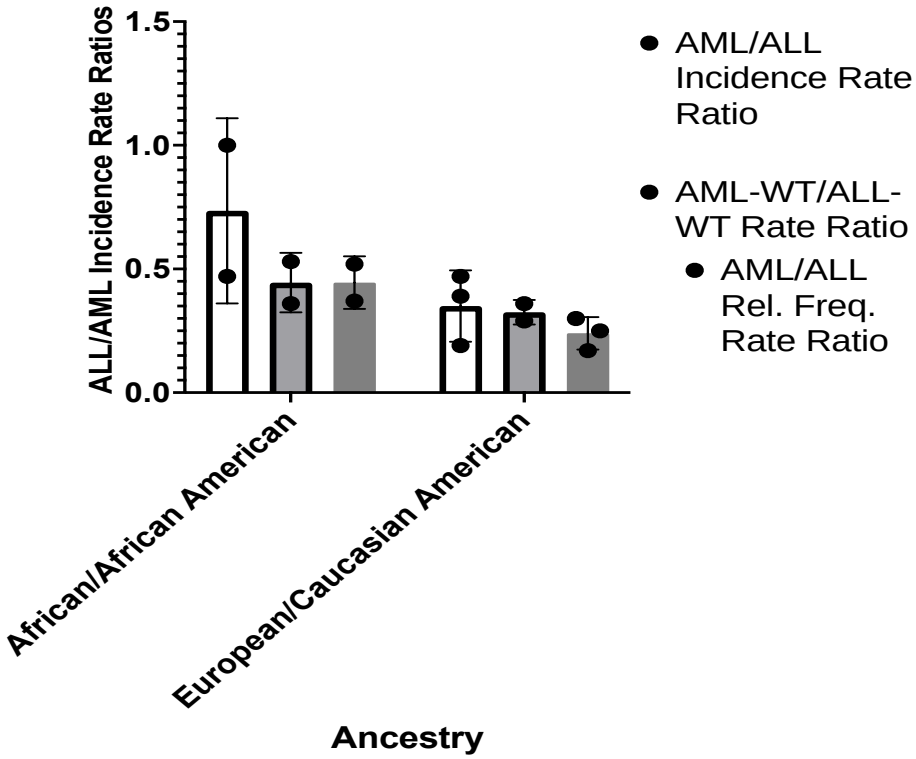
Conclusion

The environment of much of Africa, which has, for millennia, been dominated by rampant agents of infections, of which malaria is the best known, as well as other infectious agents, some of which are even postulated to be extinct.[10] These natural phenomena of the struggle between human species and the environ have led to the emergence of a variety of genetic aberrations, resulting in a spectrum of diseases.

This report is based on investigations comparing the clinical and epidemiological features of selected cancer types in Nigeria and other African populations with those of ethnically mixed populations of the US and UK. In the process, a number of assumptions have had to be made. The disease incidence that has been used to compare the disease patterns in Ibadan, Nigeria with other parts of the world, have had to be estimated due to lack of reliable census data. In spite of the fact that the Ibadan data were collected at a time of less precise technology, for example, the use of Leitz Ortholux II fluorescent microscope in the absence of modern devices like the flow cytometer, and the use of first generation monoclonal antibodies, sheep[53] and mouse[54] blood cells for immunophenotypic characterization of cells,

instead of the more sensitive and precise reagents of today. These limitations, notwithstanding, the results are not too disparate from current clinical experience. CML, for example, diagnosed with the routine technology of the 1980 African laboratory, though not confirmed by modern cytogenetics and molecular biological testing for Philadelphia chromosome and/or BCR/ABL gene rearrangement studies, manifested the clinical behaviour not unlike elsewhere. In fact, CML served in this study as an "internal control," being the only hematological malignancy not to show evidence of the influence of the lifestyle in any of the populations studied (see Figures 2 and 8, and Table 2), including being the only disease without evidence of time-space clustering (Table 1 and Figure 13). In this connection, a study of the frequency and clinical impact of ETV6/RUNX1, AF4-MLL, and BCR/ABL fusion genes on features of acute lymphoblatic leukemia at presentation, assessed at another Nigerian medical institution, concluded that the presence of these genetic markers had no impact on the clinical and laboratory features of the disease at presentation at the center.[172]

Figure 12: Childhood AML/ALL Incidence-Frequency Ratios in Africans and African Americans Compared with European and Caucasian American

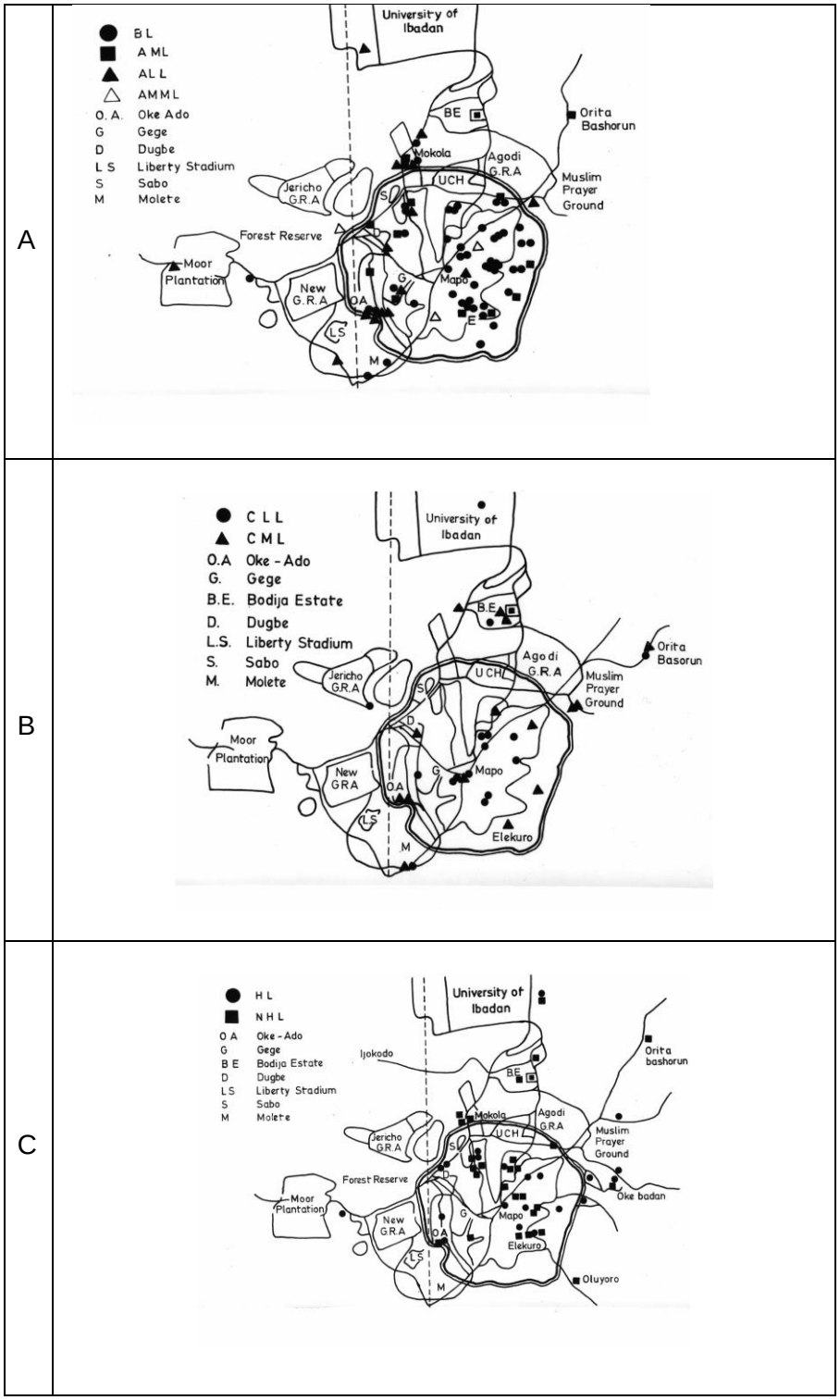


Source of Variation	% of total variation	P value	P value summary	Significant?	
Interaction	7.512	0.5026	ns	No	
Row Factor	34.59	0.0302	*	Yes	
Column Factor	19.27	0.2076	ns	No	
ANOVA table	SS (Type III)	DF	MS	F (DFn, DFd)	P value
Interaction	0.04106	2	0.02053	F (2, 8) = 0.7506	P=0.5026
Row Factor	0.1890	1	0.1890	F (1, 8) = 6.912	P=0.0302
Column Factor	0.1053	2	0.05267	F (2, 8) = 1.926	P=0.2076
Residual	0.2188	8	0.02735		

These findings, which date back to the 1980s, need to be re-evaluated and clarified with modern technology, updated population data sets, and refined diagnostic methods. A lot has changed in Nigeria over the last four decades. However, the social structure that underlies the dysparities described in this paper remains unchanged in much of the present-day Ibadan as in much of Nigeria. The global community still has much to learn about the factors that influence the dysparaties of acute lymphoblastic leukemia, acute myeloid leukemia, Hodgkin disease, chronic lymphocytic leukemia and non-Hodgkin lymphoma as described in this study. Some findings reported here indicate the influence of the African genetic ancestry in acute myeloid leukemia etiology, while socioecomic status is linked to the etiology of childhood acute lymphocytic leukemia, as well as variant of chronic lymphocytic leukemia, and chloroma-associated acute myeloid leukemia. Incidentally, the dysparities observed in African Americans compared to their compatriots of other geographical ancestry[96] are explainable by several observations in this report. These observations are suggestive of the existence of pathways to etiological discoveries in the leukemias. There is still much to learn about the role of HTLV-1 in the health and diseases of Nigerian and other parts of Africa, where the retrovirus is endemic,[173] and remains a source of health challenges to a population of over a billion.These include the safety of blood product provision services in the major endemic zones of Africa,[174-176] as well as the potential of disease control when a vaccine is finally developed against the retrovirus.[177-179]

After centuries of reductionistic explanation of disease dysparities among diverse segments of mixed populations in terms of qualities of genetic endowments, as well documented in colonial territories of Africa and the Americas, resulting in reference to "the virgin soil theory," physicians are increasingly directing their attention toward social determinants of health for answers.[180,181]

Figure 13: Localization[72] Of Disease Cases



A: ALL: Double line: Boundary of the high-density (Zone 1) quarter; Zone 2, e.g., O.A.; B.E: Zone 3 (see Methods).

Figure 14: Representative areas of Zone 1, the sprawling high-density quarter with iconic rust-roof buildings, marked with double-ring around Mapo; Zone 2 area around O.A.=Oke Ado; and the highbrow Zone 3 area of B.E. = Bodija Estate (see Figure 13).

Zone 1	
Zone 2	
Zone 3	

Conflict of Interest Statement:

None

Acknowledgement Statement:

None

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