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NARRATIVE REVIEW

Environmental determinants of leukemia and lymphoma: lessons from African epidemiology and global transition

Christopher K. Williams[1,2,3,5*], Marcus I. Asuquo[4]

[1]Department of Haematology, College of Medicine, University of Ibadan, Ibadan, Nigeria
[2]University College Hospital, Ibadan, Nigeria
[3]Hematology Oncology Consultancy, Victoria, British Columbia, Canada
[4]Department of Hematology, University of Calabar, Calabar, Cross River State, Nigeria
[5]906-379 Tyee Road, Victoria, BC, V9 A 0B4, Canada

*ckowilliams@gmail.com

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ABSTRACT

Childhood leukemia and lymphoma display striking global heterogeneity that cannot be explained by genetic ancestry or diagnostic access alone. African populations, historically characterized by high infectious burden, nutritional stress, and poor sanitation, exhibit a markedly different spectrum of hematologic malignancies from high-income countries, including reduced incidence of common/pre–B acute lymphoblastic leukemia, absence of the early childhood acute lymphoblastic leukemia peak incidence, and increased prevalence of Burkitt lymphoma and chloroma-associated acute myeloid leukemia. Drawing on African epidemiologic data and global comparative studies, this review examines how environmental factors across the life course—particularly maternal health, intrauterine exposures, early-life infection, immune programming, and socioeconomic transition—shape leukemogenic pathways. We place these observations in the context of contemporary models of leukemogenesis that recognize prenatal initiation of preleukemic clones with postnatal environmental modulation of disease progression. As low- and middle-income countries undergo rapid epidemiologic transition, understanding how improvements in sanitation, nutrition, and population mixing may alter leukemia incidence is increasingly relevant for prevention strategies. African experience thus provides a natural experiment for elucidating environmental contributions to leukemogenesis with implications extending well beyond the continent.

Keywords: Leukemia, Lymphoma, lifestyle, socioeconomic, milieu, incidence, environment, leukemogenesis.

Introduction

The discovery in 1958 of Burkitt lymphoma[2] provided the first evidence of a linkage between environmental factors and cancer. The environmental factors consisted of rain forests extensively infested by malaria-parasite carrying mosquitoes[3]. The discovery revolutionized the understanding of human cancers globally[4-7], leading to numerous cancer control strategies, some of which are still in application today. 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[3]. The question that followed was whether the African environment played a role in other cancers as well.

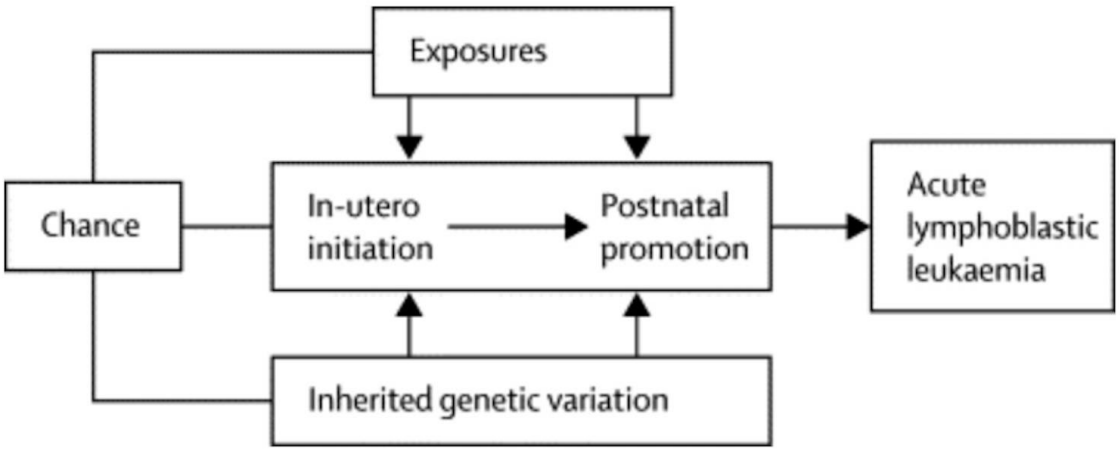
Although the incidence of childhood cancers is similar throughout the world, major differences exist in many parts of the world with respect to childhood malignancies[8]. For example, the features of childhood leukemia and lymphoma in low-income African countries are different from those of children in the high-income countries. These differences include: the rarity of the acute leukemia below the age of 5 in the former, unlike the peaking of the incidence in the 2-5 year age-group in the latter[9-12]. Although the incidence of acute myeloid leukemia in children varies little, there is considerable variability in its clinical manifestations in various parts of the world, being frequently associated with solid-tumor formation (chloroma) in developing countries, leading to its being designated as "chloroma-associated acute myeloid leukemia (CA-AML/AMML)"[11,13]. These observations, along with those associated with Burkitt lymphoma, are suggestive of the influence of variable environmental factors.

Pathogenesis of leukemia and lymphoma

ACUTE LEUKEMIA

Acute lymphoblastic leukemia, probably like other acute leukemias, and, indeed, cancers in general, evolves from interactions between exogenous (e.g., infection), or endogenous (e.g., inflammation, oxidative stress) exposures, genetic (inherited) susceptibility, chance, and the hemopoietic cell[14-25] at various stages of its development, see Figure 1. Thus, the challenge is to identify the relevant exposures and inherited genetic variants and identify how and when these factors contribute to the natural history of acute lymphoblastic leukemia, and indeed, other related hematological malignancies, from initiation (usually in utero) through the largely covert evolution to overt disease[14,26]. More than 20 candidate exposures that contribute to childhood leukemia have been identified through epidemiological and case control studies[14,16], but very few of these findings are based on reproducible data or are biologically plausible.

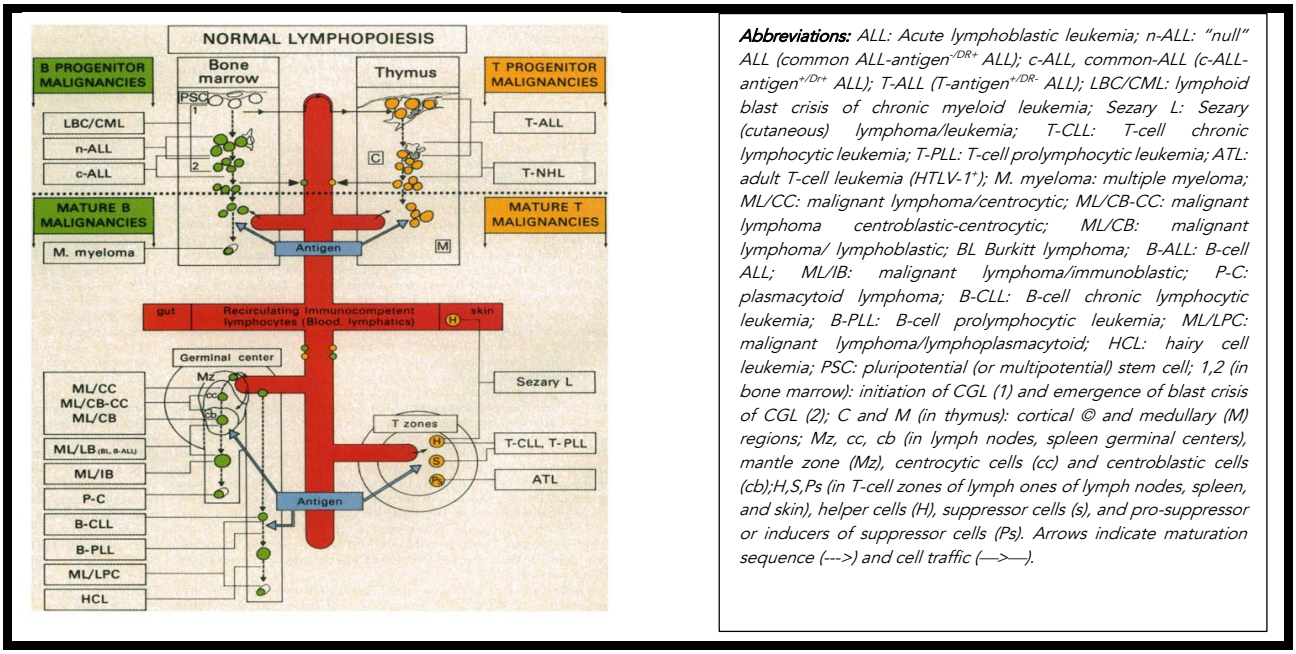
Figure 1: Composite causality of childhood acute lymphoblastic leukemia



Copied from Hiroto Inaba, Mel Greaves, and Charles G. Mulligan[14]

Infection, which was the first causal exposure for childhood acute lymphoblastic leukemia[23] remains the strongest candidate. While, unlike observations in leukemia in some animal species, no single transforming virus has been identified[16], continued exploration of possible biological mechanisms has been advocated as this could lead to prophylactic interventions[14].

Figure 2: Developmental levels of clonal amplification in lymphoid malignancy[27]



Abbreviations: *ALL: Acute lymphoblastic leukemia; n-ALL: "null" ALL (common ALL-antigen$^{-/DR+}$ ALL); c-ALL, common-ALL (c-ALL-antigen$^{+/Dr+}$ ALL); T-ALL (T-antigen$^{+/DR-}$ ALL); LBC/CML: lymphoid blast crisis of chronic myeloid leukemia; Sezary L: Sezary (cutaneous) lymphoma/leukemia; T-CLL: T-cell chronic lymphocytic leukemia; T-PLL: T-cell prolymphocytic leukemia; ATL: adult T-cell leukemia (HTLV-1^{+}); M. myeloma: multiple myeloma; ML/CC: malignant lymphoma/centrocytic; ML/CB-CC: malignant lymphoma centroblastic-centrocytic; ML/CB: malignant lymphoma/ lymphoblastic; BL Burkitt lymphoma; B-ALL: B-cell ALL; ML/IB: malignant lymphoma/immunoblastic; P-C: plasmacytoid lymphoma; B-CLL: B-cell chronic lymphocytic leukemia; B-PLL: B-cell prolymphocytic leukemia; ML/LPC: malignant lymphoma/lymphoplasmacytoid; HCL: hairy cell leukemia; PSC: pluripotential (or multipotential) stem cell; 1,2 (in bone marrow): initiation of CGL (1) and emergence of blast crisis of CGL (2); C and M (in thymus): cortical © and medullary (M) regions; Mz, cc, cb (in lymph nodes, spleen germinal centers), mantle zone (Mz), centrocytic cells (cc) and centroblastic cells (cb);H,S,Ps (in T-cell zones of lymph ones of lymph nodes, spleen, and skin), helper cells (H), suppressor cells (s), and pro-suppressor or inducers of suppressor cells (Ps). Arrows indicate maturation sequence (--->) and cell traffic (—>—).*

Not all leukemias and lymphomas are represented. The nomenclature used here for lymphoma is that of the Kiel system (see [28]). Adapted from Melvyn F. Greave.s[27]

Most human lymphoid cancers maintain gene expression patterns that are characteristic of their origins and developmental level of clonal expansion and maturation arrest[27]. In the human lymphoid lineages, there is a picture of sequential changes of membrane antigenic phenotype[29], and rearrangement and expression of immunoglobulin and T-cell receptorgenes[30,31] that accompany normal B and T lymphocyte maturation[29]. Thus, a lymphoid malignancy like the acute lymphoblastic leukemia is a biologically and clinically diverse disease[27,32].

This variation, combined with the relative rarity of the disease, compromises epidemiological studies aimed at identifying causal associations. Etiological clues can, however, be derived from comparing national incidence rates[33-35]. The major phenotypic characteristics of acute lymphoblastic leukemia (ALL) cells, which are identifiable by monoclonal antibodies, are referred to as "cluster of differentiation (CD) in the process of immunophenotyping of the leukemic cells. Such a process can, for example, yield the following phenotypic characterizations: (1) common (c) pre-B acute lymphoblastic leukemia (ALL) subtype with peak incidence in 2–5-year-old children in high-income countries shows exclusive prevalence in high-income countries; (2) a less frequent phenotype shows features of T-lymphocytes and thus, is typed T-ALL.

Childhood T and B precursor ALL subtypes have been identified by standardized immunophenotyping in different geographical and ethnic settings[36]. Comparison of the relative frequencies and estimated incidence rates of the major subtypes indicates very similar values, with the striking exception of black childhood populations in Africa, in which there appears to be a significant and selective deficit in the incidence of the common (B-cell precursor) subset of ALL. There is suggestive evidence for a similar bias in ALL subtypes in South Africans of mixed ethnic origin and in Mapuche Indians of Chile. Several interpretations of these data are possible, but the one favored among them attributes these differences primarily to socio-economic factors and patterns of infection in infancy[33,36].

THE LYMPHOMAS

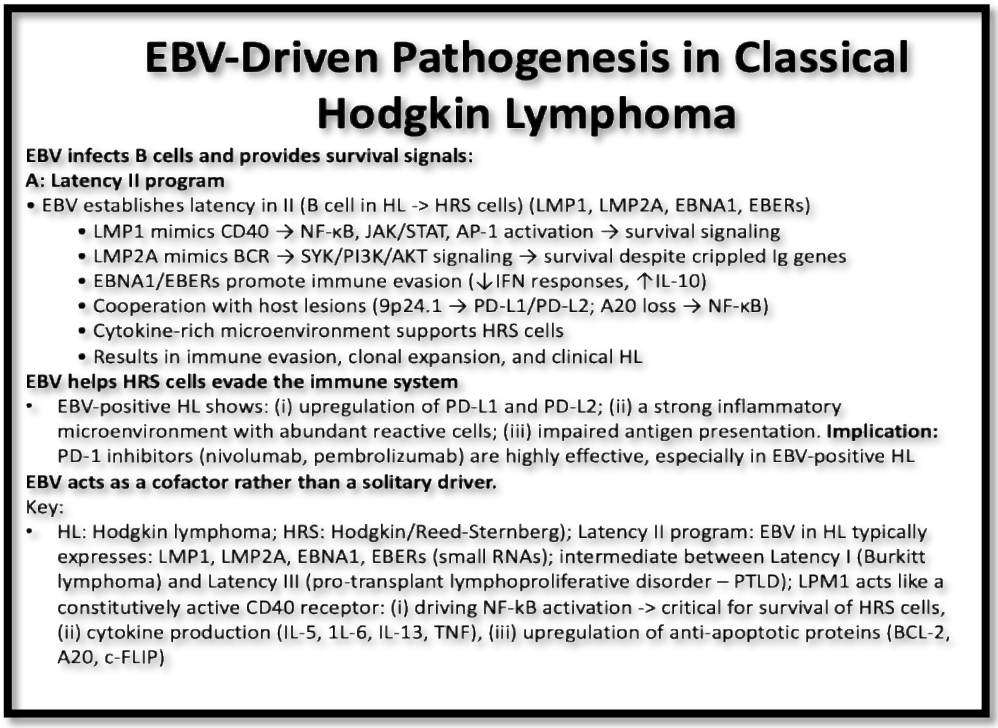
Microbials that are known to play a role in lymphomogenesis include the Epstein Barr Virus (EBV), which was discovered in association with Burkitt lymphoma[4]. Its role in endemic BL was recognized as that of "acting on a target B-

lymphocyte population altered by hyperendemic malaria, an essential co-factor responsible for the climate-dependence of tumor, to give rise either to especially large numbers of transformed B cells or to B cells transformed in an unusual way[37], such that repeated cell divisions increase the likelihood of one or another of three specific chromosomal translocations[38] 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[39,40], where it would be affected by the Ig gene promoter with subsequent selection of a *myc* oncogene-driven clone of malignant BL cells"[41]. 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[3].

HODGKIN LYMPHOMA

Ebstein Barr Virus (EBV) also plays a role in the pathogenesis of Hodgkin lymphoma (HL)[42-48] (Figure 2). Classical HL (cHL) shows EBV positivity in ~40-50% of cases in Western countries and up to 80-90% in many low- and middle-income countries, including much of Africa. EBV-positive HL is significantly more common among children and young adults in endemic regions, including Africa. EBV infects germinal-center B cells and establishes a Latency II program characterized by expression of LMP1, LMP2A, EBNA1, and EBERs. LMP1 mimics constitutive CD40 signaling, activating NF-κB, JAK/STAT, and AP-1 pathways, while LMP2A provides surrogate B-cell receptor signaling, permitting survival of crippled B cells lacking functional immunoglobulin genes[43,45,49-53]. EBV cooperates with host genetic alterations, including 9p24.1 amplification, to upregulate PD-L1/PD-L2 and promote immune evasion[54-56]. The resulting cytokine-rich inflammatory microenvironment supports Hodgkin/Reed–Sternberg (HRS) cell survival and clonal expansion. EBV acts as a critical cofactor rather than a solitary oncogenic driver, providing a biological basis for the marked efficacy of PD-1 checkpoint inhibition in EBV-positive Hodgkin lymphoma, indeed, a virus with a unique epidemiology and global relevance. Although EBV promotes survival and immune evasion, additional factors are necessary, including chromosomal gains on 9p24.1, JAK/STAT pathway activation, somatic mutations, and host immune status (HIV, immunosuppression)[43,44,48].

Figure 2: The role of Ebstein Barr Virus (EBV) in the pathogenesis of Classical Hodgkin lymphoma[42-48]



THE CITY OF IBADAN, NIGERIA

The Nigerian city of Ibadan of the 1980s (Figures 4 and 5) presented several attributes that made it a convenient milieu for the exploration of possible role of socio-economic factors in the epidemiology of leukemia and lymphoma in children and young

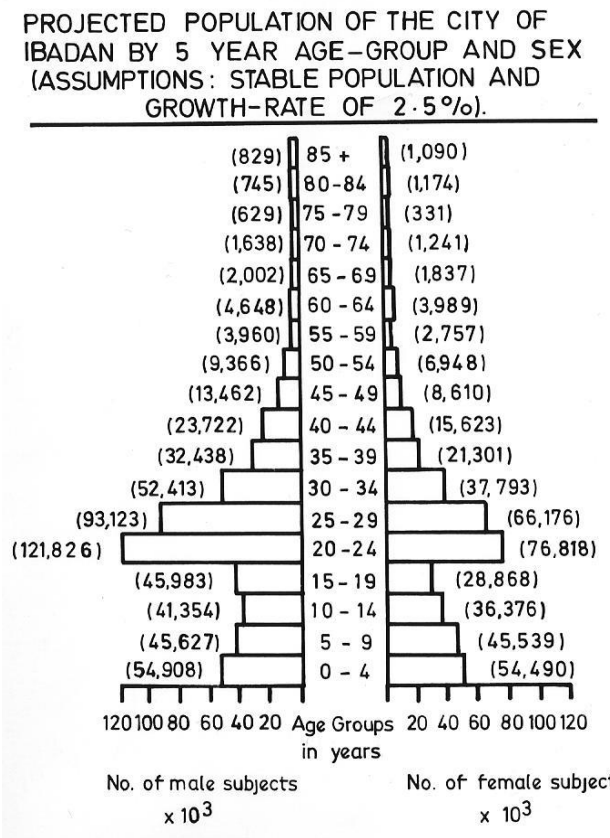
adults. It was a unique human habitat, representing a mixture of modern lifestyle of elite professionals and academics living within short distances from poorly educated farmers and artisan workers, whose lifestyles in unplanned rural-like communities hardly differed from those in nearby poorly accessible farmlands: all these within a vast area believed to be one of the largest populated urban areas in Africa[57,58]. It is also the home of one of the leading universities of Africa: the University of Ibadan, established in 1948[57,58]. 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[59-66]. Thus, it was a unique theatre of studies of the influence of the African environment and carcinogenesis.

The purpose of this manuscript is to show that the disparities 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 differential capacity of its inhabitants to mitigate the impact of these factors on their health.

Materials and 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%,[59] 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 about 1million inhabitants.

Figure 3: Projected Population of the City of Ibadan, Nigeria by age-group, in the 1980s



Population structure of the City of Ibadan in the 1980s, projected from the closest population census data of 1963, assuming a growth rate of 2.5% per year (see Methods above, and Williams and Bamgboye.[67]

ESTIMATING POPULATION SIZES FOR DERIVATION OF DISEASE INCIDENCE

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[68] and international bodies[69] 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[69] and (D) by assuming a constant growth rate since 1963 at 5% and age distribution according to the World Bank studies[69]. The estimated lowest and highest incidence values are then taken to represent the range of incidence[67].

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 hematoxylin-eosin stained paraffin section, or the presence of cytoplasmic vacuolation of the lymphoid cytoplasm[70]. 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[36], lymphoblasts derived from tumor 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 leukemia and lymphoma and films prepared therewith were routinely processed with May Gruenwald Giemsa stain, and, in cases of acute leukemia, 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 more than 20.0×10^9/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 Leukemias and Lymphomas as outlined by Greaves et al[33], using a panel of first-generation reagents including: J5[71] and AL2[72], both anti CALLA; DA 2, an anti HLA DR[73], WT 1, an anti T[74] and OKT11a, an anti E rosette receptor[75]; and My906, an anti-myeloid[76] monoclonal antibody. A large 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[77]; anti T subset murine monoclonal antibodies, including OKT3, OKT4, OKT6, and OKT8[78,79]. The binding of the monoclonal antibodies to target cells was determined by indirect immunofluorescence with fluorescein-labelled 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[80] and mouse red blood cells[81], 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 ALL. The subtypes of ALL 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[36], however, with some modifications as outlined by Borowitz[82]. 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[83].

ESTIMATING LEUKEMIA AND 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[68,69,84] 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[57,68,85] 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, inhabited mainly by indigenes of the city, most of them were farmers, petty traders, and semi-skilled laborers. 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).

Zone 2: non-indigenous high-density area inhabited by mixed population of businesspeople, petty traders, professionals, skilled and unskilled laborers from various parts of the country, mainly from the neighboring Yoruba-speaking States of the Federation of Nigeria. The level of education was generally higher than in the indigenous areas. The average annual income is intermediate between those of Zones 1 and 3.

Zone 3: low/medium population density areas, consisting largely of parkland estates and predominantly inhabited by businesspeople, academics, and professionals. 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.

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 handworkers (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 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[86] and Onibokun et al.[68] 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[69] 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 disorder was defined as at least two cases occurring within 2 km and 6 months of each other.

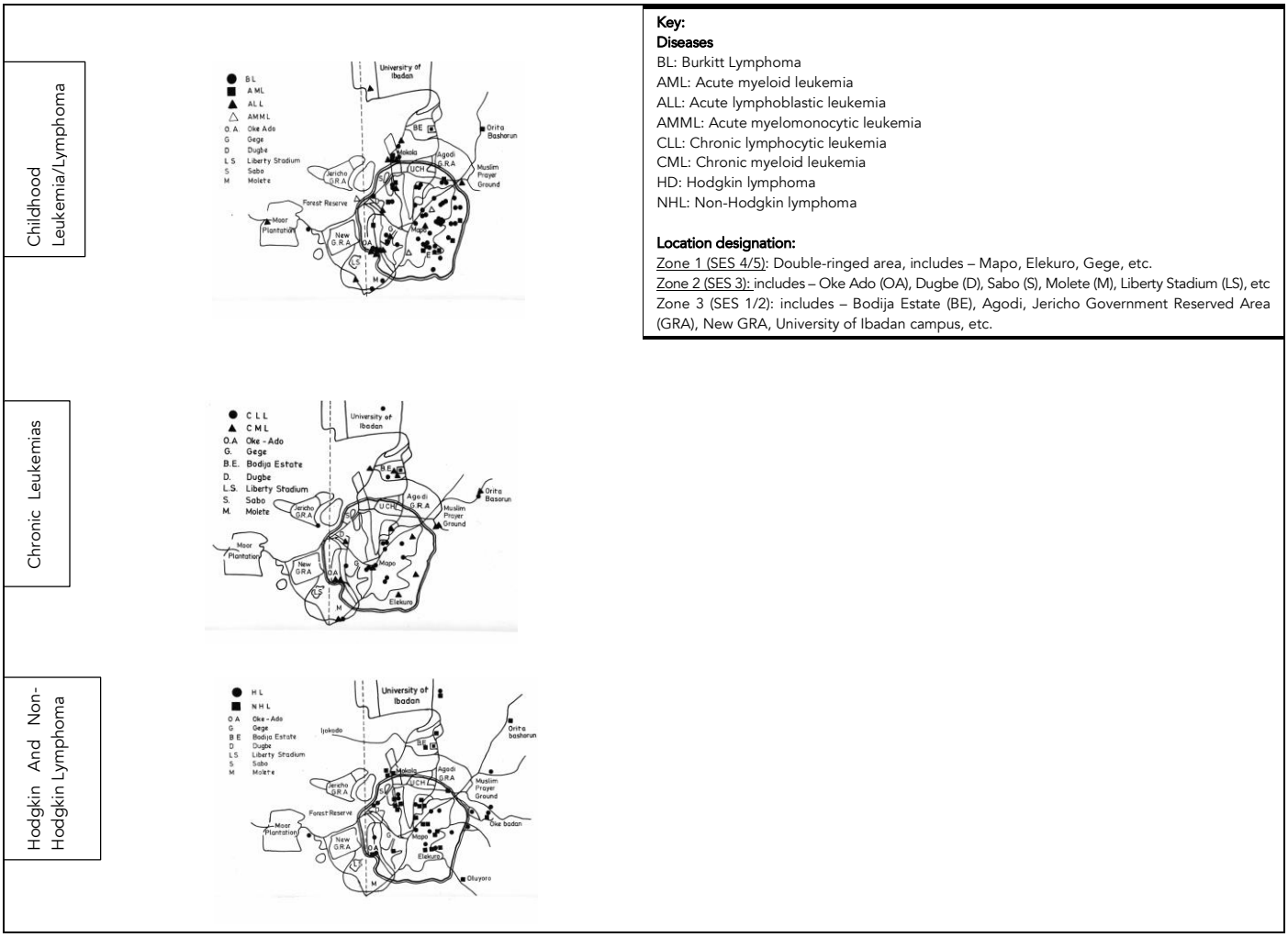
Figure 4: The City of Ibadan of the 1970s-1980s, with its zones of habitation

Zone 1: (left panel), characterized by "a sea of iconic red roofs;" Zone 2: (middle panel), surrounding Zone 1, and Zone 3, (right panel) consisting of leafy well-planned environment, (also see text for "Socioeconomic and Clustering Studies.")

Results

Cases of leukemias and lymphomas observed at the University College Hospital, Ibadan, Nigeria between the latter half of 1978 and earlier half of 1986 have previously been analyzed and published with a view to shed light on some of the unique clinical and laboratory features of these diseases in a tropical locale[1,9-11,13,67,85,87-114]. A breakdown of cases seen during the period and covered in the analysis presented in this publication are shown in Table 1. With the goal of evaluating the epidemiological

Figure 5: Disease location and socioeconomic status in haemopoietic malignancies in Ibadan, Nigeria (1979–1986)



features of these diseases through the comparison of their incidence with international observations, the incidence rates were derived using the number of cases observed over the stated period of time in the estimated patient populations projected as described in Williams and Bamgboye[67] and as shown in Figure 3.

Table 1: Cases of leukemias and lymphomas observed at the University College Hospital, Ibadan, Nigeria between the latter half of 1978 and earlier half of 1986

	Diseases	#
1.	Acute myelogenous leukemia (AML)	33
2	Acute lymphoblastic leukemia (ALL)	34
3	Chronic myeloid leukemia (CML)	44
4	Chronic lymphocytic leukemia (CLL)	31
5.	Hodgkin lymphoma (HL)	69
6.	Burkitt lymphoma (BL)	113

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

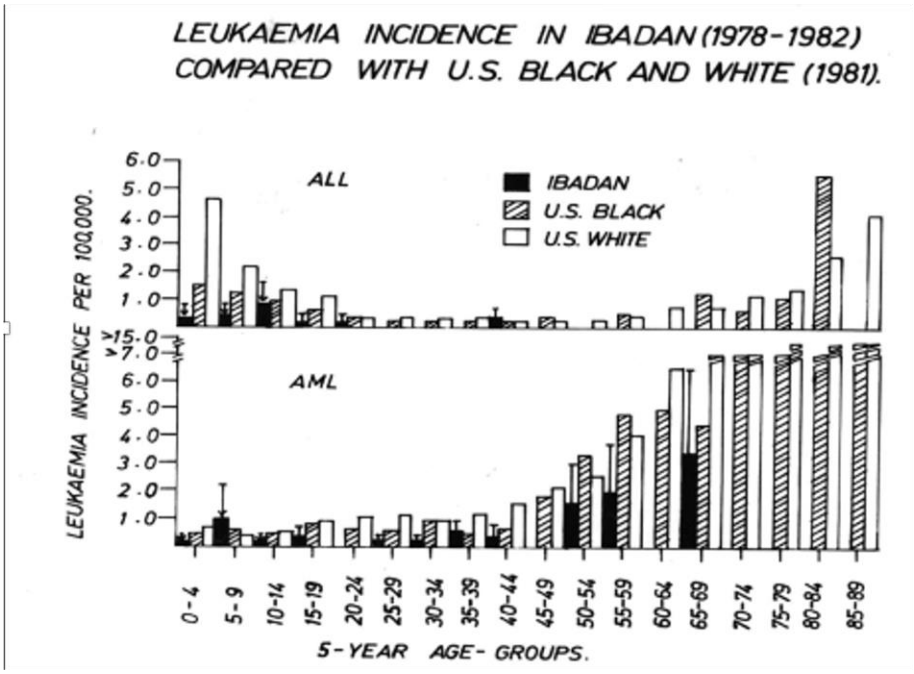
Table 2A: Incidence of Leukemia and Lymphoma Classified By The Socioeconomic Status (SES) In Residents of Ibadan, 1979 -1986

		Low (SES 4/5)	Medium (SES 3)	High (SES 1/2)
Disease	Age range in years	[Number of cases] and incidence[a] ($\times 10^{-5}$)		
BL	<15	[51] 1.81–3.62	[1] 0.21–0.42	[0] 0.0
ALL	<15	[8] 0.25–0.50	[3] 0.56–1.13	[4] 0.75–1.51
AML	<15	[13] 0.41–0.82	[1] 0.18–0.37	[1] 0.18–0.37
ALL	≥15	[4] 0.11–0.22	[0] 0.0	[0] 0.33–0.67
AML	≥15	[7] 0.20–0.39	[1] 0.16–0.33	[1] 0.16–0.33
CML	≥15	[11] 0.17–0.33	[2] 0.18–0.36	[2] 0.18–0.36
CLL	≥15	[14] 0.20–0.41	[1] 0.09–0.17	[1] 0.09–0.17
HD	<15	[6] 0.19–0.37	[2] 0.42–0.85	[0] 0.0
HD	≥15	[16] 0.50–1.00	[9] 1.70–3.40	[0] 0.0
NB/NHL	0–80	[25] 0.42–0.83	[3] 0.30–0.60	[2] 0.20–0.40

Key to abbreviations: see Figure 5.

population sizes, criteria A and B (see Methods) appear to have considerably underestimated the population sizes of the first 3 quinquennia[67]. Thus, the lowest

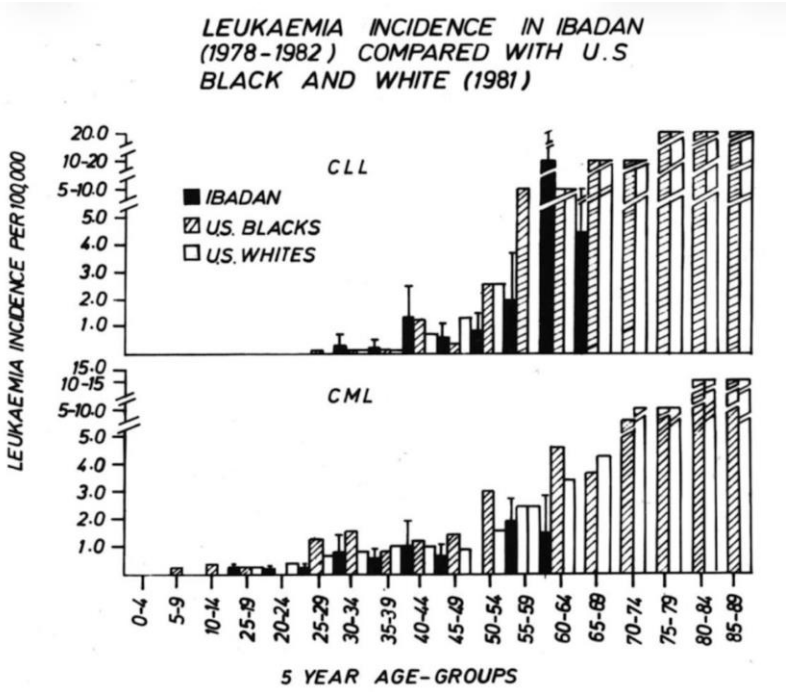
Figure 6: Leukemia incidence in Ibadan (1978-1982) compared with US Black and White (1981). The data for US Blacks and Whites were obtained from SEER[115]



The leukemia incidence in Ibadan (1978-1982) compared with US Black and White (1981)[115]. Bars on the Ibadan columns represent the estimated upper and lower range of leukemia incidence in Ibadan. The downward pointing arrows indicate that the lower limits of leukemia incidence in the first 3 quinquennia are probably lower than shown by histograms[67].

incidence rates of the leukemia subtypes in childhood are unknown but believed to be lower than the lower values obtained, hence the down-pointing 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 8. 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

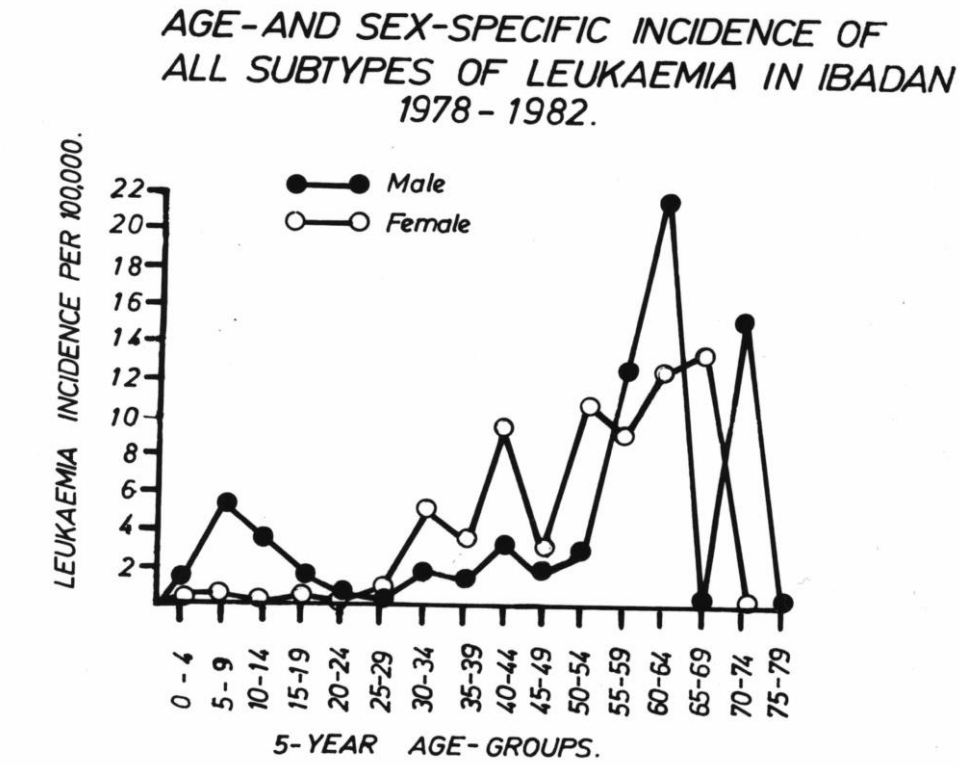
Figure 7: Incidence of chronic leukemia in Ibadan, 1978-1982 compared with US Blacks and Whites of 1981[115]



The leukemia incidence in Ibadan (1978-1982) compared with US Black and White (1981)[115]. The downward pointing arrows indicate that the lower limits of Ibadan leukemia incidence in the first 3 quinquennia are probably lower than shown by histograms[67]. Data for US Blacks and Whites were obtained from SEER 1981[115].

predominance. The age- and sex-specific incidence of all leukemia subtypes observed in Ibadan in 1978-1982 shown in Figure 8 reflects the marked prevalence of acute myeloid leukemia and acute lymphoblastic 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[67].

Figure 8: Age- and sex-specific incidence of all subtypes of acute lymphoblastic leukemia in Ibadan (1978-1982)



INTRA-CITY LOCALIZATION AND SOCIOECONOMIC STATUS OF LEUKEMIA AND LYMPHOMA CASES IN IBADAN (1979 – 1986).

The distribution of cases as well as the incidence of leukemias and lymphomas in localities of Ibadan are shown shown in Figure 4. Most striking is density of cases of childhood leukemia and lymphoma within the double-ringed enclosed area of the city, shown in left panel of Figure 5, which is the Zone 1 (see Materials and Methods), an area of poor sanitation inhabited by families living on an estimated income of $1,000 or less (SES 4/5) annually. The most common hematological malignancy in the locale was Burkitt lymphoma, the incidence of which, at 1.81-3.62 (Table 2A), is about 9 times higher than the immediate adjacent area outside the double-ring, namely the Zone 2, which was inhabitedd by families living on more than $2,000 (SES) annually. Zone 3, which is roughly located some 2 to 5 kilometers (e.g., the campus of the University of Ibadan, located in the upper most part of each panel) did not have a single case of BL and the incidence of the disease there was zero. Table 2 shows that 13 of 14 cases of clustering involving BL cases occurred within Zone 1, compared to one incidence of BL clustering, which occurred in Zone 2. These observations are consistent with the influence of poor sanitation and poverty in the causation of BL, as illustrated in Figure 10.

Childhood ALL showed the opposite pattern of distribution compared to BL with the its incidence in the Zone 3 areas of the city, where individuals of SES 1+3 lived, with childhood ALL incidence of 0.75 – 1.51 (Table 2A), about three-fold the rate of Zone 1. As shown in Figure 10, there is a striking link between childhood ALL in Ibadan and the SES gradient of its inhabitants, indicating a role for environmental ecology. Childhood AML (including acute myelomonocytic leukemia [AMML]), which tended to be associated with chloroma (i.e.,

chloroma-associated AML) (Figure 13), was, with the incidence of 0.41-0.82) (Table 2A) more than twice as frequent in Zone 1 as in Zone 3 where its incidence was 0.18-0.37). Its increased frequency in the 2nd quinquennium in Ibadan children (Figure 13), probably contributed to the incidence peak for AML seen in Figure 6 and Figure 8. The incidence of Non-Burkitt/Non-Hodgkin lymphoma was, with 0.42-0.83 was twice as high in the population of SES 4/5 (Zone 1) as compared to those of SES 1/2 (Zone 3) (Table 2A) (Figure 5).

Chronic myeloid leukemia shows a remarkable similarity of incidence in all SES groups (Figure 10), and shows no evidence of clustering (Figure 5). Hodgkin lymphoma in <15 and ≥15 children also shows a link to SES gradient, its incidence being at least twice as high among SES 3 compared to SES 1+2 (Figures 5 and 10).

Table 2: Occurrence of clustering of cases of hematological malignancies in areas of Ibadan, Nigeria, 1978 – 1983 (see Figure 5)

	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.

INTERNATIONAL COMPARATIVE STUDIES

The availability of incidence data for Ibadan residents, even though only as crude estimates, has enabled a comparison with leukemia rates in other geographic climes and populations[67]. This is particularly relevant to the United States (US), with its population diversity, including its inhabitants of African descent, as well as the excellent cancer data bank in form of the Surveillance, Epidemiology and End Results (SEER) higher than in Ibadan children, while in the second quinquennium, the acute myeloid leukemia incidence rate in Ibadan is highest of the three populations. The acute lymphoblastic leukemia incidence in the second quinquennium in US Caucasian (White) children is at least twice as high as in Ibadan children. Acute lymphoblastic leukemia 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 (chloroma-associated acute myeloid leukemia), which afflicted boys of this age group (see Figure 6 and Figure 12 – right panel). Thus, while both Caucasian American and African American children show peak ALL incidence in the first quinquennium, a peak incidence of ALL is delayed to the 15–19-year age-group, and by age gradient, among the Ibadan children and young adults (Figure 15).

Figure 6 and Figure 7 show a comparison of leukemia incidence rates in Ibadan in this study with those of contemporaneous African (Black) and Caucasian (White) American populations. Figures 6 and 7 show that the pattern of leukemia incidence in the three populations studied were essentially similar. 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 lymphoblastic

leukemia incidence rate in Caucasian (White) Americans and African (Black) Americans are at least 5- and 2.5-fold respectively.

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 among Ibadan patients, different compared to the American rates. The remainder of the observations beyond age 69 is probably due to survival differences.

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 6 and Figure 7, the pattern of the incidence of all immunophenotypes of these three populations[11,116,117,120-122] is extended to include those of the United Kingdom (Figure 9). Although the incidence of ALL 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.

Table 3: Pattern of acute lymphoblastic leukemia subtypes in Nigerians, United States, UK and Malaysia, including number of cases and frequency (%)

	Ibadan/Nigeria*		USA (Caucasians)**		United Kingdom©		African Americans®	Malaysians$
Age-groups in years	<15	≥15	<15	≥15	<15	≥15	<15	<15
c-ALL	4 (22.2)	8 (38.1)	217 (74.4)	37 (47.4)	398 (73.2)	23 (54.8)	16 (55.2)	7 (50.0)
Null ALL	2 (11.1)	1 (4.8)	21 (7.2)	?	68 (12.5)	11 (26.2)	4 (13.8)	2 (21.4)
T-ALL	7 (38.9)	11 (52.4)	45 (15.5)	20 (25.6)	73 (13.5)	5 (11.9)	9 (31.0)	4 (28.6)
B-ALL	4 (22.2)	1 (4.8)	8 (2.7)	?	4 (0.7)	1 (2.4)	0 (0.0)	0 (0.0)
Unclassifiable	1 (5.6)	0 (0.0)	0 (0.0)	21 (26.9)	0 (0.0)	2 (4.8)	0 (0.0)	0 (0.0)
Total	18 (100)	21 (100)	291 (100)	78 (100)	542 (100)	42 (100)	29 (100)	14 (100)

*Data based on this report; ** Data based on;[116] ® Data based on;[116]© <15 Data based on,[117] ≥15 data based on;[118] $ Data based on[119]

Table 4: Comparative incidence (number of new cases per annum x 10^{-5}) of subtypes of acute lymphoblastic leukemia in Nigerian, United Kingdom and US children

Leukemia subtypes	Nigerian	United Kingdom	US Caucasian	African American
ALL (all subtypes)	0.8[b]	2.61[c]	2.46[d]	1.26[d]
c-ALL	0.18[c]	1.91[f]	1.83[f]	0.70[g]
T-ALL	0.31[d]	0.35[f]	0.36[f]	0.40[g]
B-ALL	0.18[e]	0.02[f]	0.06[f]	0.0[g]

b,[123] c,[121,122] e: derived from b,[144] and data in Table 3 f: derived from c and the data in Table 3, g: derived from d and the data in Table 3.

Thus, the incidence of the T-ALL subtype served as an internal control, indicating that the reduced incidence of other ALL 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 ALL 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. A correlation of the incidence of leukemia and lymphoma,

Figures 9, 10, 11: Population- and socioeconomic-specific patterns of hematological malignancies of childhood and young-adulthood in Ibadan, Nigeria, 1978 – 1986

Figure 9

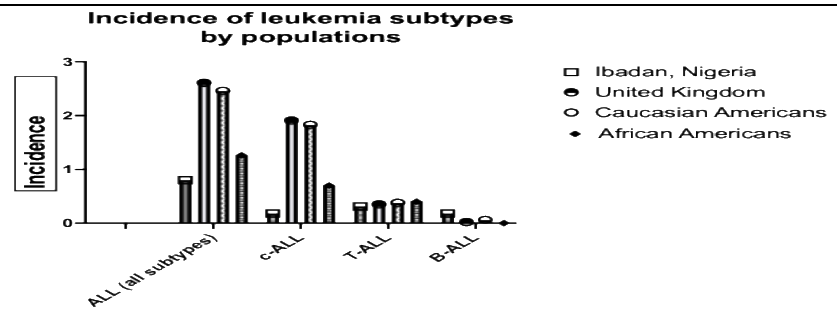


Figure 10

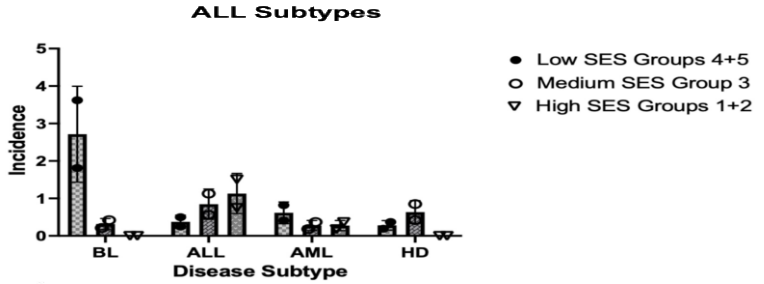
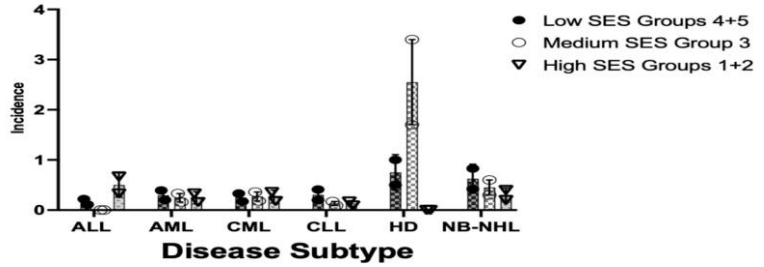


Figure 11

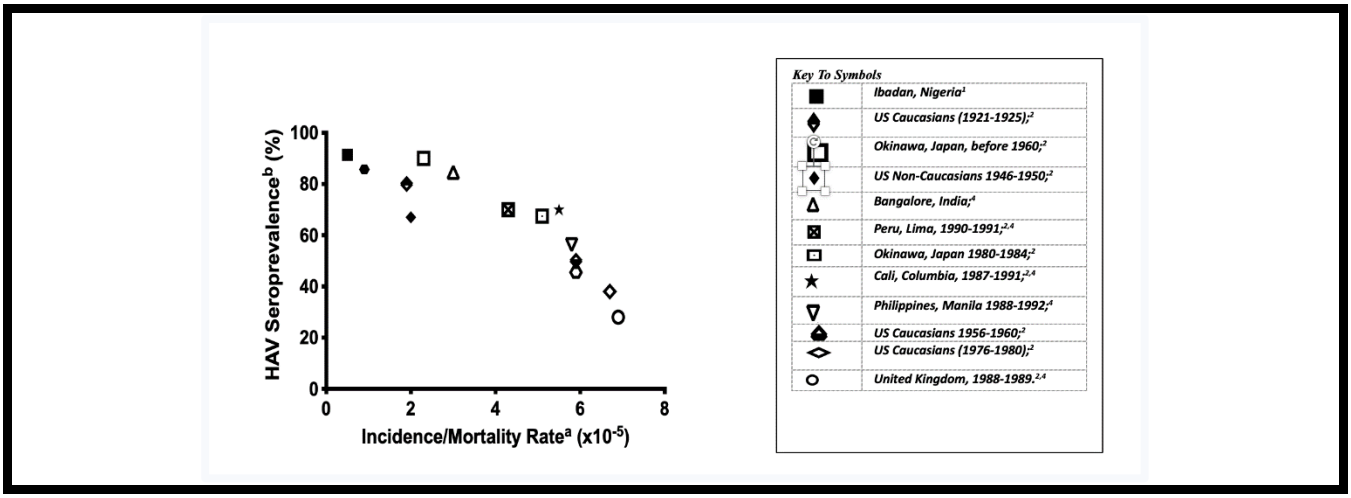


Key: ALL: acute lymphoblastic leukemia; c-ALL: common pre-cursor ALL; BL: Burkitt lymphoma; AML: acute lymphoblastic leukemia; HD: Hodgkin lymphoma; CML: chronic myeloid leukemia; CLL: chronic lymphocytic leukemia; NB-NHL: Non-BL Non-Hodgkin lymphoma

Main features: (i) reduced incidence of ALL in Nigerian children is largely attributable to a selective deficit of common ALL (c-ALL), while T-ALL incidence is relatively preserved, arguing against generalized under-diagnosis[11,16,101,124],(ii) ALL incidence has SES gradient; (iii) BL and AML are related to low SES,(iii) HD show higher SES; (iv) CML and CLL lack SES gradient.

based on immunophenotypic[33,76,117] and/or gene rearrangement[83,101,125] analyzed in correlation with the socioeconomic status (SES) of the patients (see Methods) aged <15 years and >15 years are shown in Figure 10 and Figure 11, respectively. In both age-range categories, there is a significant correlation between disease incidence and SES (p=0.0024 and p=0.0043, respectively). A few features appear to be striking in the

Figure 12: Influence of infection and/or sanitation on childhood acute lymphoblastic leukemia incidence in a global population



Incidence of childhood acute lymphoblastic leukemia correlated with hepatitis A virus (HAV) seroprevalence in the first decade of life, or infant mortality rate, another measure of the adequacy of public hygiene,[126] has been used as a surrogate index of HAV seroprevalence rate.[127] The correlation (Pearson) is highly significant (p value = <0.0001).

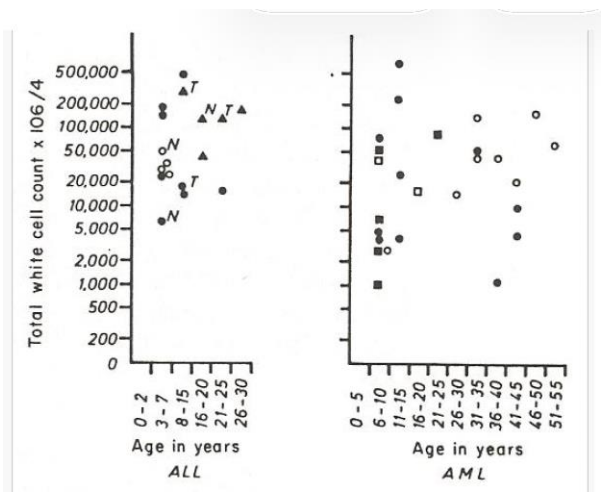
correlations between the disease incidence and SES, including the following:

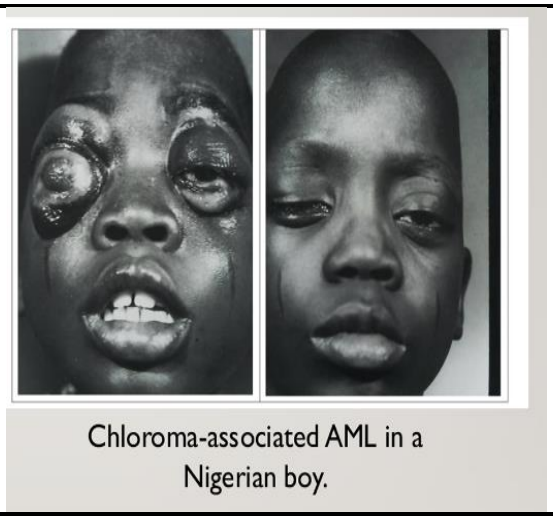
a. among children (age <15 years – Figure 10), low SES is strongly correlated with BL and AML (presumably the chloroma-associated variant).

b. among children (age <15 years – Figure 10), low SES is strongly correlated with BL and AML (presumably the chloroma-associated variant).

ALL and HD are strongly associated with rising SES (Figures 10 and 11).

Figure 13: Leucocyte count in association with tissue invasion in ALL and





Chloroma-associated AML in a Nigerian boy.

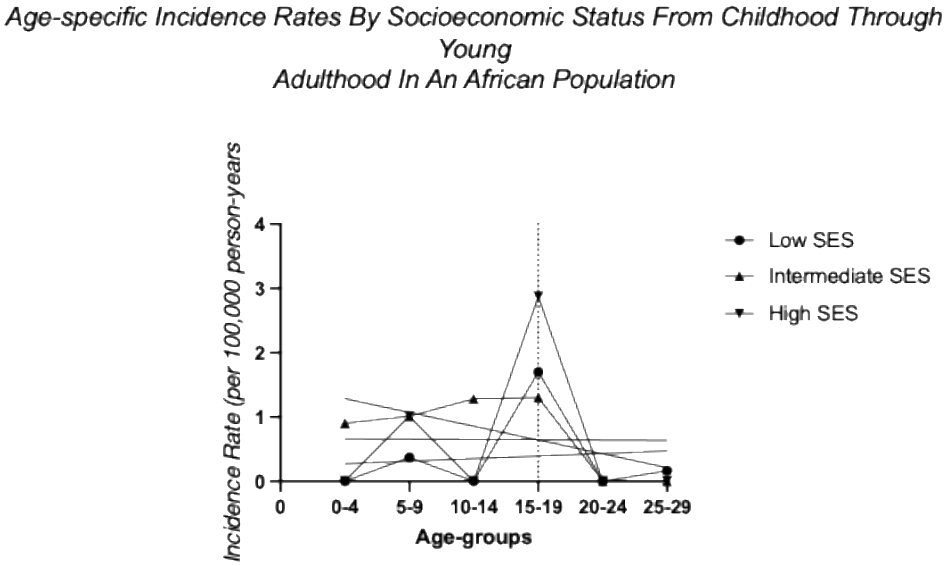
Key: White cell counts correlated with the presence of solid tumors at diagnosis of ALL and AML. Closed circles = males; open circles = females; closed triangles = ALL in males with tissue invasion, e.g., mediastinal and testicular masses; closed rectangle = AML in males with chloromas; open rectangles = AML in females with chloromas; T = T-cell ALL; N = Null-cell *ALL.*

Chloroma associated AML in a Nigerian boy aged 9 years, with involvement of both orbits, more pronounced left than right the picture on the right was at presentation, while to the left is at remission. The right panel shows that 5/8 cases of AML in the 5-10 age-group were chloroma-associated.[11]

This figure demonstrates that tissue-invasive manifestations of childhood acute leukemia—mediastinal or testicular masses in ALL and chloroma-associated AML—occur across a wide range of peripheral leukocyte counts and are not restricted to cases with extreme hyperleukocytosis[128,129].

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 (Figure 11). However, there is a correlation in CLL with low SES (Figure 11), also confirmed in Table 2, which shows clustering of CLL cases in zone 1

Figure 15: Influence of Socioeconomic Status by Age at Diagnosis



Age-specific incidence rates (see Methods) were calculated for six 5-year age bands (0–4 through 25–29 years) to characterize patterns from childhood through young adulthood and to avoid imposing an arbitrary pediatric age cutoff at 19 years. Dotted vertical line within 15–19 denotes transition to young adulthood.

e. the pattern of linkage between SES and the incidence of HD[130,131], would seem to suggest some complexity of association (see Figure 2 footnote)

Table 5: Biological model linking environmental factors to childhood leukemia phenotype in Ibadan, Nigeria – originally conceptualized by Williams[1,132]

Gross (mouse)[133,134]	Ibadan (human population)[1,135]
Undernutrition	Maternal & childhood malnutrition
Thymectomy / thymic atrophy	Thymo-lymphatic deficiency
Suppressed lymphatic leukemia	Absence of incidence peak of ALL in <5 yrs
Emergence of chloroleukemia	Increased chloroma-associated AML
Viral/infectious modulation	Malaria, measles, chronic infections

Illustration of maternal malnutrition and infection in humans, corresponding to Gross's experimental undernutrition, leading to impaired fetal growth, thymic atrophy, leading to suppression of early childhood ALL (especially c-ALL), thus, favoring (diversion from lymphoid to myeloid) leukemogenesis, including chloroma-associated AML (Figure 13). This is precisely the phenotype Gross produced experimentally, but here it occurs naturally at population scale[134,135].

Discussion

There is no documentation of the considerations that led to the choice of the City of Ibadan[57], Nigeria as the seat of first Faculty of Medicine in West Africa, when the British colonial authorities opted to create the University College Ibadan (UCI) in 1948[136,137], with a Faculty of Medicine as one of its initial faculties. In retrospect, the chosen location was exceptionally well suited for studying the environmental determinants of cancer, combining a large indigenous population, distinctive physical and ecological conditions, and significant exposure to sociocultural change driven by the influx of a western-educated elite from nearby Lagos during the pre-independence period. Ibadan soon became a vibrant intellectual enclave blossoming within a typical African urban squalor with locales and peoples of varied lifestyles (Figures 4 and 5). In the population mixture was also a cadre of intellectuals from Europe and America, some of whom had been attracted there by the opportunity of studying Burkitt lymphoma (BL), a disease that had been discovered in Kampala, Uganda in 1958[2,70,138], which shared similar ecosystem with Ibadan. Some of the earliest advances in the study of this unique cancer were to revolutionize the global insight into the nature of cancer[4,60,87].

The survey that led to the discovery of BL 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[3]. The question then was whether there were other environment-related disease entities within the milieu that yielded the discovery of BL.

Meanwhile, the heterogeneity of the childhood acute lymphoblastic leukemia (ALL)[139] was evolving, including the realization that subtypes of the disease might have different epidemiology.[117] Furthermore, emerging clinical awareness was revealing that the Ibadan population was harboring childhood hematologic malignancies with features that differed from those of high-income countries, including BL and chloroma-associated acute myeloid leukemia[123,140-142]. These observations coincided with Melvyn Greaves's evolving concepts about the heterogeneity of ALL[117] and its epidemiology, which he was exploring with his international studies of ALL subtypes. Some of the most important revelation of those studies included the observation of reduced incidence of common/pre–B ALL (c-ALL), and the absence of its early childhood peak incidence, as the signatures of childhood ALL in Ibadan, as well as in the Black children of the South African townships and the children of the Mapuche Indians of Peru[33,36,143]. These studies have served as a uniquely informative window into how childhood hematologic malignancies segregate by environmental ecology rather than "race,"[101] thereby supporting the views of others[33,144]. Three signatures stand out with particular relevance to current models of leukemogenesis: (i) a marked depletion of c-ALL among Nigerian children (22% of childhood ALL) compared with UK/US series (Tables 3), as well as Greaves et al;[124] (ii) a selective incidence deficit concentrated in non-T (especially c-ALL) pathways while T-ALL incidence is broadly preserved across populations (Table 4), and (iii) a striking, internally consistent SES/urban-density gradient within Ibadan, in which ALL increases

stepwise with SES (Figure 10), while Burkitt lymphoma and chloroma-associated AML/AMML predominate and cluster in low-SES, high-density zones (Table 2) (Figure 10). Taken together, these patterns argue that the dominant leukemogenic routes expressed in a population are modulated by the timing/intensity of early-life exposures (infection burden, sanitation, nutrition, and related immune programming), and not simply by access to diagnosis[16,26,145-148].

LEUKEMIA-LYMPHOMA CAUSING RISK FACTORS IN IBADAN, 1979-1986

Studies in both experimental animals[149-152] and humans, earlier in studies from Ibadan[153-159], and more recently confirmed by others[160-164], have established that severe atrophic changes of the thymolymphatic system are a constant feature in malnutrition, 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 was 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. It was also believed that, consequently, there had been a depletion of circulating T-lymphocytes, and that this manifested in the form of an impairment of cell-mediated immunity and increased susceptibility to infection[153,154,165].

THE GROSS EXPERIMENTS IN ANIMAL LEUKEMOGENESIS

The epidemiology of childhood leukemias in Ibadan in particular, and in Sub Sahara Africa in general, with delayed childhood peak of ALL incidence, the reduction in the incidence of the common precursor B-ALL, the relative increased incidence of the myeloid variant (Figures 6 and 8) in childhood, often in association with chloroma formation (Figure 13), were reminiscent of the observations of Gross[134] on the influence of environmental factors in animal 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 splenectomy 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 impact of maternal malnutrition and infection in humans and its correspondence to Gross's experimental undernutrition and thymectomy is outlined in Table 5. Figure 14 revisits a conceptual model first proposed four decades ago[1,13,132], depicting how malnutrition and infection may affect thymolymphatic development and modulate the incidence of childhood leukemia, updated considering current understanding of leukemogenic mechanisms. This diagram presents a proposed biological model linking environmental adversity to the distinctive epidemiology of childhood leukemia observed in Ibadan, Nigeria. Maternal malnutrition and maternal infection (e.g., malaria) are proposed to impair fetal growth[166] and thymic development, resulting in thymo-lymphatic deficiency[155,167-169]. This state, further reinforced by early-life infections and protein–calorie malnutrition[165,170], is hypothesized to suppress the emergence of acute lymphoblastic leukemia (ALL) in the first two quinquennia of life[16,33,101], while favoring myeloid leukemogenesis, including chloroma-associated acute myeloid leukemia (AML)[134,140,141]. The model mirrors classic experimental observations by Ludwig Gross, in which undernutrition and thymic impairment suppressed lymphatic leukemia and permitted myeloid or chloroleukemic phenotypes in mice[134]. Thus, the Ibadan childhood leukemia pattern may represent a natural human analogue of these experiments, mediated by environmental and developmental pressures rather than genetic differences[133,134].

In today's terms, the Ibadan observations fit naturally into a "prenatal initiation + postnatal promotion" framework: prenatal preleukaemic clones are likely generated universally,[125,129,131] but the probability of progression to overt disease—particularly BCP/c-ALL—may depend on immune training and inflammatory context[16,127,166,171] shaped by sanitation and infection ecology (Figure 12), while BL reflects a distinct but overlapping ecology of chronic immune stimulation (e.g., malaria/EBV)[3,144,171]. The Ibadan SES gradient anticipates the contemporary epidemiologic transition in many African settings, where improving sanitation and changing contact patterns can shift disease spectra toward the classic childhood ALL peak even as other environmentally

linked malignancies recede[101,172,173]. A priority now is to pair population-based ascertainment with modern immunophenotyping and genomics to test whether the historically "missing" burden corresponds specifically to lesions typical of affluent settings (e.g., hyperdiploidy/ETV6–RUNX1), and to resolve whether CA-AML/AMML (Figure 13) represents a distinct biology or a context-dependent presentation phenotype—work that would convert this rare epidemiologic signal into actionable prevention and early-diagnosis strategies[26,33,123,134,147,172,174].

MATERNAL-FETAL PROGRAMMING

The living conditions of Nigeria in the 1980s and 1990s have been characterized as being between 0.321 and 0.438, i.e. within the "Low Human Development" category[175], probably with marked variability within the one-million people city of Ibadan. It has been stated that it is difficult to distinguish between the effect of prenatal conditions and those of genetic inheritance or postnatal "investments" in children[166]. The impact of low human development is transmitted intergenerationally through maternal disadvantage, whereby health at birth is an important predictor of long-term outcomes, including education, income, and disability[166]. While up to 5–10% of childhood ALL and a larger fraction of infant leukemia have in utero–initiated clones, often involving ETV6–RUNX MLL (KMT2A) rearrangement, these preleukemic clones are necessary but not sufficient for leukemogenesis. Postnatal "second hits" determine progression, and improving fetal health reduces the creation, expansion, or survival of preleukemic clones. Periconceptional folate reduces the risk of ALL ≈15-30%, while adequate vitamin B12 and B6 supports DNA methylation stability. This is particularly crucial in Sub Sahara Africa, where folate deficiency remains common.

THE GREAVES HYPOTHESIS AND INTERPRETATION OF THE IBADAN DATA

The Greaves hypothesis, widely accepted for acute lymphoblastic leukemia (ALL), proposes that leukemogenesis involves a prenatal genetic lesion followed by an aberrant immune response to infection in early childhood. This framework explains how environmental exposures, varying across geographic and socioeconomic contexts, shape distinct epidemiological patterns of childhood hematologic malignancies. The Ibadan data show that the reduced childhood ALL incidence (Figure 9) is driven mainly by depletion of precursor B-lineage/c-ALL and loss of the under-5 peak, with relative preservation of T-ALL (Figure 8), and that hematologic malignancies segregate by SES/urban density in opposite directions (c-ALL vs BL/CA-AML) (Figures 5,10,11). The most parsimonious explanation is that environmental conditions linked to deprivation and high pathogen load alter early immune development and the likelihood of progression of prenatal preleukemic clones, while simultaneously promoting BL through malaria/EBV ecology. CA-AML/AMML's high frequency and clustering (Table 2) suggests additional environment–host interactions (immune milieu, coinfections, hematopoietic stress) and/or diagnostic pathway effects that warrant targeted study. These observations anticipated current interest in how early-life immune programming and environmental exposures shape leukemia subtype risk during epidemiologic transition[134,140,141,145].

The main conclusion of the Ibadan data, that environmental/lifestyle pressures outweigh "race/ethnicity" as an explanation of subtype patterns is supported by: (1) strong between-population differences in c-ALL proportion (Figure 9), (2) within-population SES gradients in ALL and BL (Figure 10), and the plausibility of immune-infection ecology affecting progression of prenatal clones. These observations from the "natural experiment"[176-178] of environmental ecology of Ibadan are consistent with the Gross experiments[134] as a useful conceptual analogue for how sustained environmental stressors (nutrition, infection burden) can shift the balance of lymphoid vs myeloid pathways and alter clinical phenotypes (Table 5, Figure 14); the Ibadan observations are consistent with such a shift, though the mediating immune and nutritional pathways require direct measurement in contemporary cohorts.

EPIDEMIOLOGIC TRANSITION IN NIGERIA AND OTHER LMICS

When placed alongside the Ibadan data, Table 6 supports a coherent temporal narrative, whereby 1980s–early 1990s, the Human Development Index of Nigeria was ≈0.411-0.438 (low HDI). This implies that life expectancy was short, schooling was limited, infection burden was high, leading to

suppressed incidence of c-ALL, the absence of under-5 peak of the incidence of ALL, dominance of Burkitt lymphoma and chloroma-associated AML. In the period of 2010s-2020s, the country was transitioning, with improved survival, education, and income, reduced early childhood infections, and altered timing of immune challenges. The prediction is that these changes might have ushered in an emergence of c-ALL along with age-shifted ALL incidence, as well as gradual decline of deprivation-linked malignancies, such as Burkitt lymphoma and chloroma-associated AML. This is consistent with the recent reports of declining frequency of BL cases in Ibadan, assuming a minor role of ascertainment in the reports[179,180].

Table 6: HDI transition in Nigeria from 1980-1990 to 2015-2025

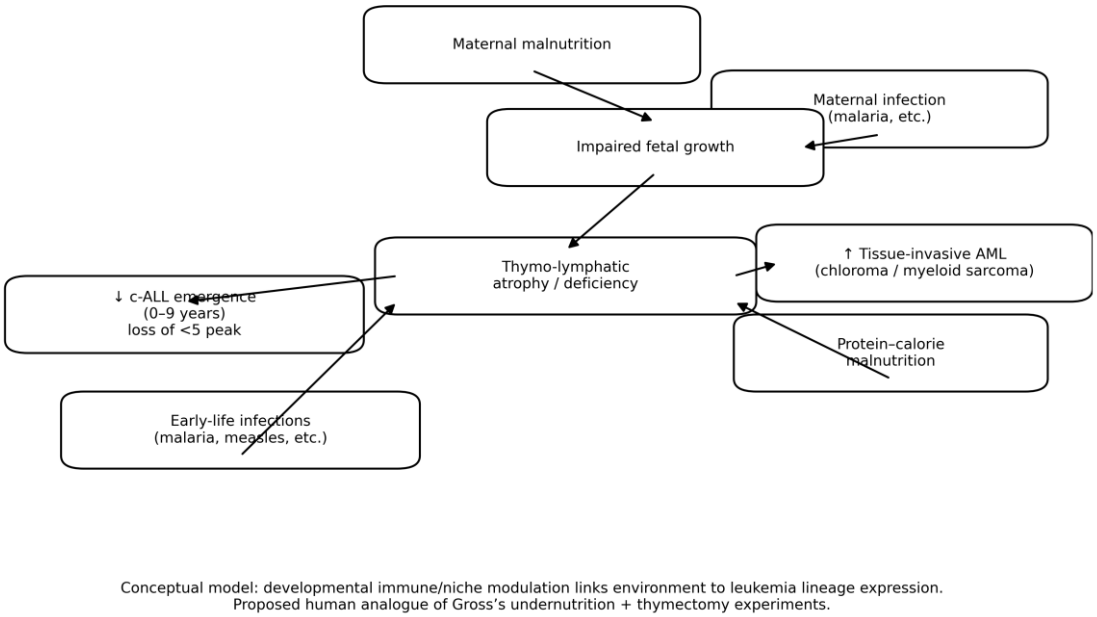
Determinant	Approximate value / status 1980-1990	Approximate value / status 2015-2025	Notes / Change over time
Human Development Index (HDI	~ **0.411-0.438** in 1990 (Low HDI)	~ **0.548-0.560** in recent years (2022-2025), moved into Medium HDI in ~2025	HDI has improved ~25-30% from 1990 to mid-2020s, though still in the lower-half globally
Life expectancy at birth (total population)	~ ≈ **45.9 years** in 1990	≈ **52-55 years** in mid-2020s (e.g. ~54.5 yrs in 2023)	Increase by ~8-10 years. Still low compared to many peers
Expected years of schooling	~ **6.7 years** in 1990	~ **10.0 years** in 2015-2020 range	Large improvement in schooling expectations
Mean years of schooling	~ **2.0-2.8 years** in 1990 (depending on source; ~2.79 yrs)	~ **6.0-6.2 years** by ~2015-2020 period	Significant gains in schooling retention or completion over time.
GNI per capita (PPP)	In **1990**, approx **US$1,900** (current PPP) or ≈ **US$3,067** in constant 2011 international dollars PPP	In more recent years (~2020-2023) around **US$5,000** in current PPP or around **US$5,300+** (constant dollars) depending on year.	More than doubling in per capita PPP income since 1990 (though inflation, inequality, and real purchasing power vary regionally).
Life expectancy gain	Life expectancy relatively flat in many years in 1980s, only small gains in the early part of the 1990s	More steady upward trend through 2000s and 2010s; continuous, though incremental, improvements in recent years	The rate of increase has improved, though health shocks (e.g. epidemics, COVID) complicate the trend
Other determinants (education, health expenditure, etc.)	Secondary school enrolment low; public health expenditure low; unemployment and foreign exchange instability major issues; per capita income relatively low.	Education expenditure rising (though % of GNI still modest), health service coverage improving, expected years of schooling higher	Overall improvement, but many challenges remain: inequality, unequal access, service quality, etc.

This table documents a clear and sustained improvement in Nigeria's human development indicators between roughly 1980–1990 and 2015–2025, spanning income, education, and survival. Although Nigeria remains in the lower half of global rankings, the magnitude of change—particularly in life expectancy (+8–10 years), schooling (mean years rising from ~2–3 to ~6 years), and HDI (~25–30% increase)—is epidemiologically meaningful.

In this light, the table is not merely descriptive socioeconomic data—it provides biological plausibility for why childhood ALL incidence might be expected to rise[13], change subtype distribution, and shift age patterns as Nigeria continues its development trajectory[101].

When interpreted alongside the within-city socioeconomic gradient in childhood ALL incidence observed in Ibadan, the documented national improvements in Nigeria's human development indicators provide a coherent temporal framework for leukemogenesis. In the 1980s, low life expectancy, limited schooling, and low income were associated with early, intense infectious exposure and chronic immune activation, coinciding with suppression of childhood ALL—particularly the common/pre–B subtype—and absence of the under-five incidence peak. As human development indicators improved over subsequent decades, the environmental conditions that historically constrained ALL emergence have progressively shifted. The age-dependent increase in the incidence of ALL among higher socioeconomic strata within Ibadan thus represents an early manifestation of the broader national transition documented by rising HDI, education, and survival. Together, these observations suggest that socioeconomic development operates as a population-level modifier of leukemia risk by altering postnatal immune and inflammatory contexts rather than by introducing new genetic susceptibility. Importantly, the changes documented here are sufficient in scale to move populations across the threshold at which leukemia epidemiology historically changes. Similar HDI and life-expectancy inflection points preceded the emergence of the classic childhood ALL peak in mid-20th-century Europe and Japan[181-184].

Figure 14: Environmental and developmental modulation of childhood leukemia phenotype: a proposed human analogue of Gross's leukemogenesis experiments[134,135].



RELEVANCE OF IBADAN CLINICAL DATA TO CONTEMPORARY BIOLOGY OF LEUKEMOGENESIS

Although the epidemiologic observations from Ibadan were generated several decades ago, their relevance is strengthened rather than diminished by subsequent advances in molecular biology. It is now well established that initiating lesions in childhood leukemia frequently arise prenatally and are detectable in healthy newborns, implying that population-level differences in incidence must largely reflect postnatal modifiers of disease progression. The internally consistent socioeconomic and age-related gradients observed within a single urban African population, coupled with preserved incidence of T-lineage ALL, argue strongly against diagnostic under-ascertainment or ethnic genetic explanations. Instead, these findings support a model in which socioeconomic development alters immune ecology in early life, selectively permitting progression along specific leukemogenic pathways. The documented improvement in national development indicators (Table 6) further suggests that such transitions are ongoing and biologically consequential.

The epidemiology of childhood acute lymphoblastic leukemia (ALL) in Ibadan, Nigeria provides a rare within-population demonstration that leukemia risk is shaped by environmental context and socioeconomic transition, rather than genetic ancestry or diagnostic access alone. The observed stepwise increase in the incidence of across socioeconomic strata, coupled with a marked age shift in disease emergence (Figures 10 and 15), reveals a biologically constrained pattern that is difficult to explain by ascertainment bias. Notably, children from the lowest socioeconomic strata show a pronounced depletion of ALL—particularly in early childhood—while higher socioeconomic groups account for most cases, with incidence rising preferentially in older children. Preservation of T-lineage ALL incidence across populations further supports subtype-specific environmental modulation rather than global under-diagnosis.[33,123] When interpreted alongside national human development trends, these findings assume broader temporal significance. Between the late 20th century and the mid-2010s, Nigeria experienced substantial improvements in human development indicators, including gains in life expectancy, education, and per-capita income, reflected in a ~25–30% increase in the Human Development Index. Although absolute levels remain modest, the scale of change is epidemiologically meaningful and parallels transitions previously observed in Europe, North America, and post-war Japan prior to the emergence of the classic early childhood ALL peak[16,127]. These improvements serve as proxies for altered early-life immune ecology—reduced infant mortality from infection, improved sanitation and housing, delayed timing of common infections, and changes in nutrition and healthcare access.

Together, the within-city SES gradient and national development trajectory support a coherent biological model in which prenatal initiation of preleukemic clones is common, but progression to overt ALL is gated by postnatal immune and inflammatory contexts. Molecular studies have now demonstrated that key initiating lesions, including chromosomal translocations and hyperdiploidy, frequently arise in utero and may be detectable in healthy newborns[13].

Population-level differences in the incidence of ALL, therefore, likely reflect variation in postnatal selective pressures rather than differences in mutation rates. Environments characterized by early, intense microbial exposure and chronic immune activation[170]—as historically prevalent in low socioeconomic settings in Africa—may suppress progression along the common/pre–B ALL pathway while favoring alternative malignancies such as Burkitt lymphoma and chloroma-associated AML[13,185].

In this context, the Ibadan data can be viewed as an early manifestation of an epidemiologic transition in childhood leukemia. The age-dependent increase in the incidence of ALL among higher socioeconomic strata within Ibadan mirrors (Figures 10 and 15), in microcosm, the broader national shifts documented by improvements in survival and education. Similar inflection points in life expectancy and sanitation preceded rising ALL incidence in other regions, suggesting that Nigeria and comparable low- and middle-income countries may be entering a developmental window in which the burden and subtype distribution of childhood leukemia will change predictably[24,172].

Importantly, this interpretation does not imply that socioeconomic development "causes" leukemia in a simplistic or deterministic sense. Rather, it reframes childhood ALL incidence as a marker of successful public health transition, reflecting altered immune maturation and inflammatory exposures in early life. Recognizing this relationship has practical implications. As countries continue to improve maternal and child health, integration of cancer surveillance with child health programs becomes increasingly relevant. Moreover, understanding how nutrition, vaccination strategies, infection timing, and maternal health interact with leukemogenesis may ultimately inform prevention strategies that preserve the benefits of development while mitigating unintended biological consequences[168].

African epidemiologic studies, particularly those from Ibadan and national development patterns, predicted key aspects of modern leukemogenesis models years before molecular evidence confirmed them[1,9,13]. Re-examining such populations with contemporary immunophenotyping and genomics is now timely and may yield insights not only into leukemia biology, but also into how societies can navigate epidemiologic transition with foresight.

TISSUE INVASIVE NATURE OF CHILDHOOD LEUKEMIA IN IBADAN, 1979 – 1986

A common feature of childhood leukemia, the nature of which modern biology clarifies, is tissue invasiveness, which manifests as mediastinal or testicular masses in ALL and chloroma-associated AML (Table 13) — occurring across a wide range of peripheral leukocyte counts and not restricted to cases with extreme hyperleukocytosis[128,129]. The dissociation between circulating blast burden and extramedullary disease suggests that tissue invasion reflects intrinsic biological properties of leukemic cells interacting with permissive developmental and environmental niches rather than late-stage disease progression[186]. The prominence of chloroma-associated AML and the relative scarcity of early childhood common B-precursor ALL in low socioeconomic settings are consistent with environmental modulation of immune development and hematopoietic lineage expression[170,187]. These observations anticipate modern concepts of leukemic niche biology, in which chemokine signaling, adhesion pathways, and stromal interactions shape disease phenotype. Together, the data illustrate how socioeconomic transition may influence not only the incidence but also the clinical expression of childhood leukemia.

Conclusion:

Although the Ibadan observations were generated in the early 1980s, their relevance is strengthened—not diminished—by modern molecular insights. Current evidence demonstrates that key initiating lesions in childhood leukemia arise prenatally and ubiquitously[26,145,148], implying that population-level differences in incidence and subtype distribution must be driven largely by postnatal modifying factors[16]. The Ibadan dataset

is therefore uniquely valuable because it captures a population at an early stage of epidemiologic transition, where environmental contrasts (sanitation, infection burden, nutrition, and urban density) were stark yet internally comparable within a single city and diagnostic center. Importantly, the observed selective depletion of c-ALL with preservation of T-ALL, coupled with opposing SES gradients for ALL versus BL and CA-AML/AMML, provides a biologically coherent pattern that cannot be explained by diagnostic access alone. Rather, it anticipates contemporary models in which immune training, inflammatory milieu, and infection ecology shape the likelihood that prenatal preleukaemic clones progress to overt disease. Re-examining such populations with modern flow cytometry and genomics offers a rare opportunity to test whether specific molecular subtypes (e.g., *ETV6–RUNX1*, hyperdiploidy) are environmentally contingent, thereby informing prevention strategies during ongoing socioeconomic transitions in low- and middle-income countries.

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1. [5]To whom all correspondence should be directed: Christopher K. Williams, MD, FRCPC, 906-379 Tyee Road, Victoria, BC, V9A 0B4, Canada, E-mail: ckowilliams@gmail.com

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i. Drafting of Figure 2: The role of EBV in the pathogenesis of Classical Hodgkin lymphoma
ii. Drafting of Table 6: HDI transition in Nigeria from 1980-1990 to 2015-2025
iii. Modernizing a diagram visualizing the Updating a diagram to show Nature's experiment, equivalent to Gross's animal experiment. originally designed and published in 1985[1], and redrawn, with the same logic, but in contemporary style, as shown in Figure 14: Environmental and developmental modulation of childhood leukemia phenotype: a proposed human analogue of Gross's leukemogenesis experiments.

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