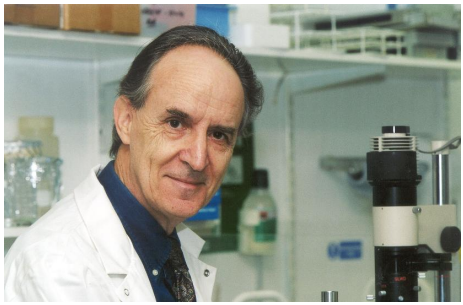
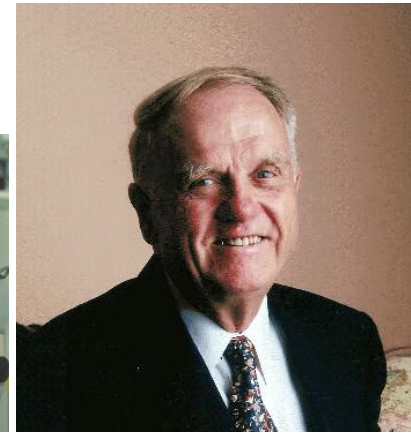
INTRODUCTION TO CHILDHOOD LEUKAEMIA

Mel Greaves and Donald Pinkel





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Leukaemia is a cancer of blood cells, as are lymphoma and myeloma. In common with all cancers, they are cellular disorders driven by mutations or modifications of DNA, our genetic code. In an individual patient with leukaemia all the leukaemic cells are a clone; the progeny of a single, disordered blood cell.

Leukaemia accounts for a modest fraction of adult cancers ($\sim 7\%$) and, although substantially rarer (by 10 fold) in children, leukaemia is the major type of paediatric cancer, accounting for around one third of all cases. Cancer occurs throughout the animal kingdom. Several mammalian species, especially domesticated cats, cattle and chickens develop leukaemia. Medical records from antiquity in Greece and India backtrack the presence of cancers from more than 2000 years ago. In that sense, cancer is not a modern disease, as often asserted. But some cancers are easier to detect than others e.g. those of the breast and skin for example. Leukaemia posed a problem in this respect. It may well have existed at some level throughout human history but in the absence of microscopy, this "liquid" cancer would have escaped detection. Patients with leukaemia then would have died of infection or haemorrhage without a diagnosis. It was therefore not until the mid-19th century (with the emergence of microscopy and cellular pathology) that leukaemia was first observed.

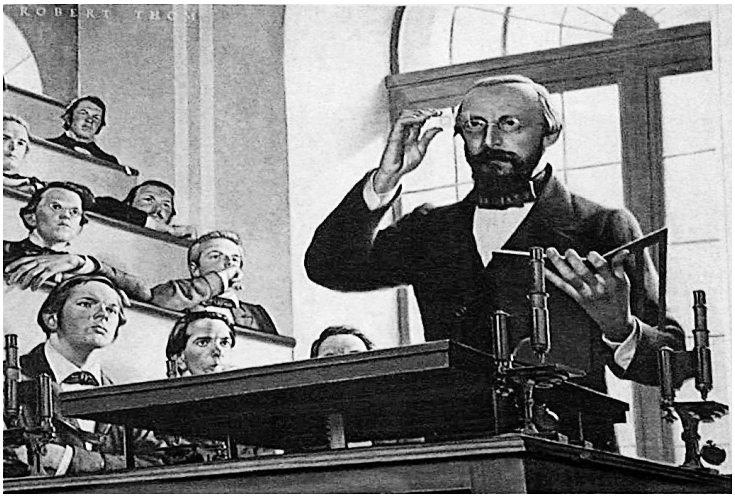


Fig. 1. Rudolf Virchow, German cellular pathologist.

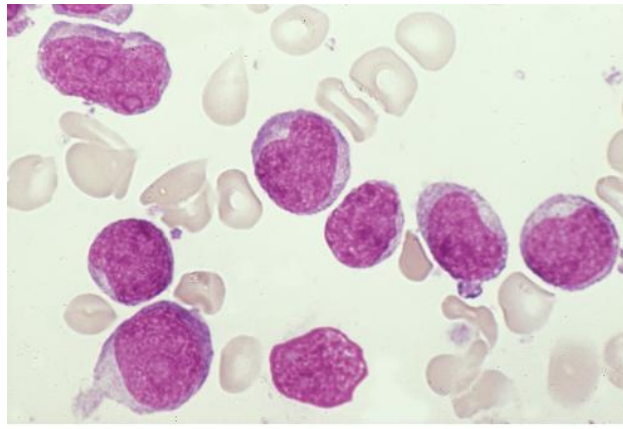
In 1845, a young medical doctor, Rudolf Virchow (Fig. 1), observed a patient with complaints of weakness and pallor. The patient had a large spleen and her blood was near white because of very few red blood cells and excessive white blood cells. He reported this case in a medical journal classifying it as a case of "white blood". He thought it was a new disease. His seniors doubted this idea; they considered this patient a victim of infectious disease. The high white blood cell levels were a reaction to infection. This opinion was similar when a French and two contemporary Scottish physicians published similar case reports.

But unlike the others, young Dr Virchow embarked on an intensive investigation of his "new" disease. He gathered more cases of this fatal disorder and studied their gross and microscopic anatomical findings as well as clinical features. A decade later he published a detailed monograph including meticulous hand drawings of what he now called "leukaemia", Greek for white blood. From these observations, he postulated the cellular theory of leukaemia. The disease was caused by uncontrolled replication of a disordered blood cell precursor with growth and survival advantages over normal blood cell

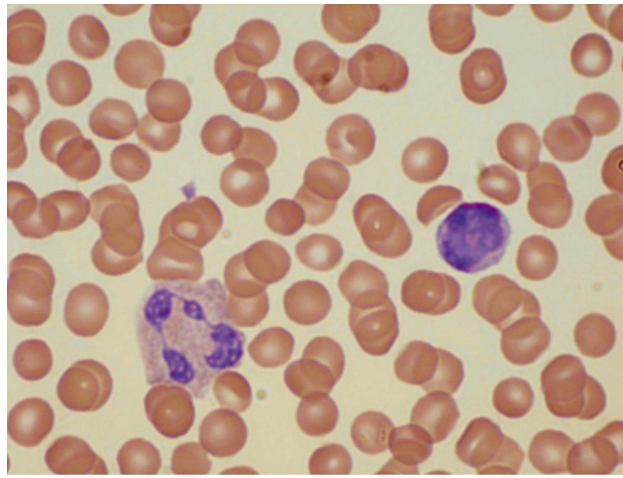
precursors. This unregulated proliferation eventually interfered with normal body function, resulting in the death of the patient. Virchow's theory remains essentially correct 150 years later. It was elaborated by newer discoveries in cell and molecular biology and genetics as highlighted elsewhere in this book.

Most of the cases of leukaemia described by Rudolph Virchow and other European pathologists in the mid-19th century were adults. From their brief descriptions and rather superficial microscopic evidence, it was probable that most of these patients were suffering from chronic myeloid leukaemias. A more detailed classification of leukaemia awaited the discoveries of Paul Ehrlich in the 1880s. Ehrlich discovered aniline dyes that could stain blood films which distinguish the morphology of different types of myeloid and lymphoid blood cells. Ehrlich, and later the Swiss haematologist Naegeli, had the insight that clinically acute leukaemia involved "primitive" cells from the bone marrow that developed into distinctive myeloid and lymphoid lineages (Fig. 2). Thus was coined the terms acute lymphoblastic leukaemia (ALL) and acute myeloblastic leukaemia (AML). Anecdotal reports of leukaemia in children appeared in the late 19th century. By the turn of the century (1904), Churchill, a physician in Chicago, had described a series of children (15 cases) diagnosed with ALL. Their duration of disease before death was short (a few days to a few months) and the age range was newborn to 10 years.

The classification of acute leukaemia in children and adults are usually two major varieties, ALL and AML. This remained grounded in the simple morphology of the dye-stained cells until the 1970s, when immunologists introduced antibodies that could reliably distinguish different types of morphologically anonymous lymphoid cells. Consequently, ALL was subdivided into subsets corresponding to B lineage precursors and T lineage precursors. In the 1980s, scientists carried out subcellular dissection of leukaemic cell diversity at the level of chromosome structure and then at the level of DNA. They discovered the critical and diverse underlying molecular pathology



(A)



(B)

Fig. 2. Leukaemic (ALL) (A) versus normal blood (B). Courtesy of Dr B Bain. (A) The nucleus of the leukaemic cells is stained red by special dyes. (B) Two normal white cells in sea of smaller red cells. Large cell lower left is granulocyte. Round cell at 3.o'clock with purple stained nucleus is normal lymphocyte.

that drives the diseases. The classification that emerges from these sequential insights over the decades is a branching tree-like structure (Fig. 3) used in the haematology laboratories of many hospitals.

Modern human genome scanning methods indicate that each patient's leukaemic cells have followed a unique evolutionary trajectory as a novel subspecies of cell. The consequence is that each

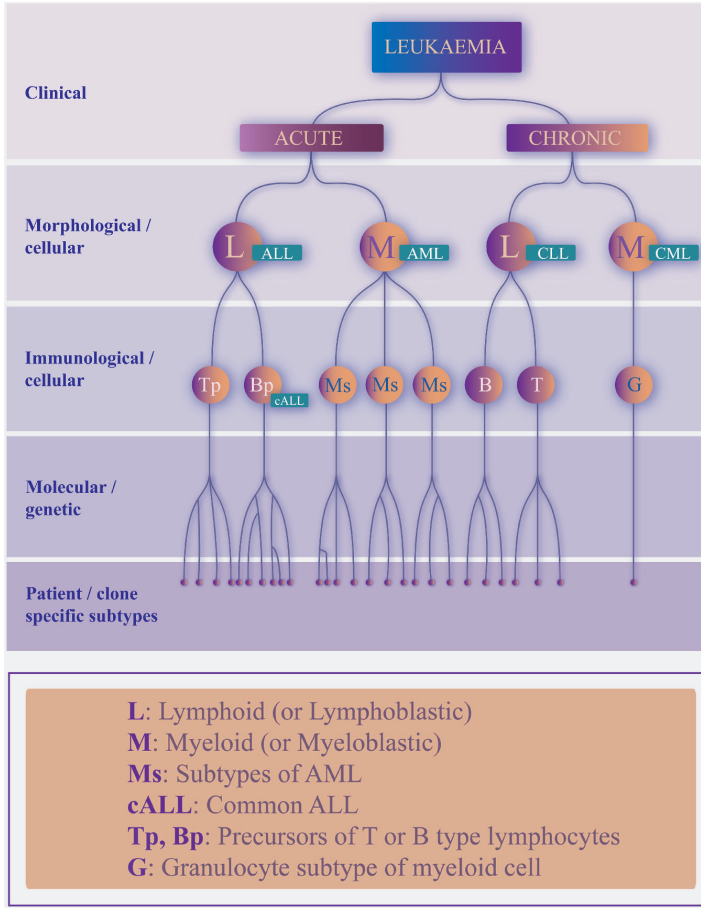


Fig. 3. Hierarchical classification of leukaemia.

patient's leukaemia ends up represented by an individual leaf on a specific twig or a particular branch of the tree. The prevalence of the major branching subtypes of childhood leukaemia vary according to age. The peak incidence of disease at ages two to five years old reflects mostly the "common" or B cell precursor variant of ALL (Fig. 4).

Most cancers probably harbour a similar degree of complexity which, in part at least, may explain some of their general intransigence to successful therapy — they are not *one* disease. The degree

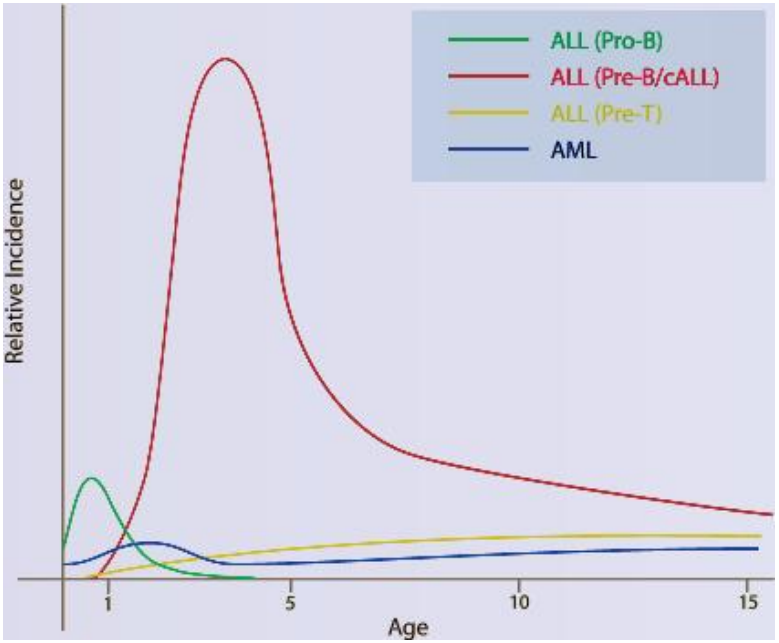


Fig. 4. Age distribution of main subtypes of childhood leukaemia.

of cellular, chromosomal and molecular diversity in leukaemia raises some difficult but important practical issues and opportunities. At what level of cellular and molecular characteristics is response to therapy determined? This must surely depend upon the particular therapy itself which has been continually modified and tailored to cellular subtype. Currently in leukaemia, and cancer in general, it appears that abnormal genotype, i.e. altered chromosomes and genes, has a major impact on clinical response and outcome. This can be rationalised as we now know that the altered or mutated genome influences the signal pathways in cells that control life or death of those cells in the face of therapeutic drugs or irradiation. The patterns of distinctive genetic change in leukaemic cells also provide potentially ideal therapeutic targets since they uniquely distinguish leukaemic from normal cells. But, this in turn poses a very considerable dilemma for cancer and leukaemia therapeutics. Do we design

and tailor novel therapeutics to match each patient — with all the technical and major financial implications this would entail — or do we continue to strive to identify shared, generic features of leukaemia that provide common therapeutic targets? Currently, both avenues are being explored very actively.

Childhood acute leukaemia occurs throughout the world, though it appears that the incidence rate of ALL is significantly higher (perhaps by 10 fold) in more affluent or developed countries. In the latter, the annual incidence rate is at around 30 to 40 cases per one million children which, for paediatric populations in the UK or the USA, translates to around 450 or 2,750 new cases each year respectively. In absolute terms, the risk of any child developing acute leukaemia between birth and age 15 years (in Europe, Australia or the USA) is approximately one in 2000.

The initial, clinical diagnosis of childhood leukaemia relates to the pathology, the common symptoms being paleness (anaemia), bleeding tendency, fatigue, aches and pains and unexplained fevers. Collectively, they reflect the highjack of normal bone marrow function by leukaemic cells. Treatment, as described in the chapter by Donald Pinkel, is now relatively complex and consists of chemotherapy with several drugs in different combinations and various schedules for approximately 3 years. In the case of Janine (Chapter 6), this was effective and curative. When standard chemotherapy fails, intensive chemotherapy using drugs and/or drug schedules not included in the initial treatment can be curative in many children.

Very high dose chemotherapy followed by haematopoietic stem cell transplant to replenish the child's blood cell system with donor graft cells (and produce an immune reaction to the leukaemia) has been used for over three decades. This procedure can be curative but is associated with a relatively high procedure-related early death rate and long term disability and late death. This negative outcome is largely due to reaction of the donor immune system to the child's normal organs and tissues but also to side effects of the drugs used to suppress the reaction. This was the case, sadly,

for Georgie whose story is told in Chapter 5. Meaningful comparisons of haematopoietic stem cell transplant methods versus intent to cure "salvage chemotherapy" for children with relapsed ALL have been conducted in the United Kingdom and the United States. They demonstrate no advantage in cure or quality of survival for transplant methods.

Despite the success in treating childhood leukaemia (cure rates are reported to be 80%) for some children with ALL, much remains to be done. Closer attention is needed to monitoring the effects of each element of treatment on growth and development of the children to healthy, happy, fulfilled adults. The eventual risk/benefit ratio of each element must be weighed and reweighed in deciding on current treatment.

The challenges for the future lie in the development of more specific biologically targeted treatment and in preventive measures derived from the understanding of the causes and mechanisms of leukaemia. Perhaps then, the many children worldwide currently without access to curative treatment will be reached.