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Observations of unprecedented remissions following novel treatment for acute leukemia in children in 1948

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Half a century ago, a diagnosis of leukemia in a child was considered a death sentence. Today, approximately 85% of children diagnosed with this once fatal disease are cured.^{1,2} The discovery that ushered in this dramatically transformed outlook was the observation by Sidney Farber (1903–1973) and his colleagues in Boston in 1948 that drugs that acted against the vitamin folic acid could produce remissions in children with acute leukemia.³ While carefully controlled studies were required to develop therapeutic regimens developed from these initial observations,^{4,5} the Farber article is featured in the James Lind Library because it is an example of a treatment effect that is so dramatic that bias can be confidently ruled out as an explanation for the observations.⁶ What led to the landmark findings in 1948, and what evidence was published subsequently confirming that a major advance in treatment had been discovered?

White blood

Gordon Piller⁷ reviewed the history of leukemia, which means ‘white blood’ in Greek. In 1811, Cullen reported a case of ‘splenitis acutus in which the serum of the blood drawn from the arm had the appearance of milk’.⁸ A spate of more detailed reports appeared in the 1840s — in Paris,⁹ Edinburgh,^{10,11} Berlin,¹² and London.¹³ Symptoms included fever, enlarged spleen, swollen lymph nodes, and a proliferation of ‘purulent matter and lymph’¹⁰ in the blood that, under a microscope, showed a ‘large number of colourless granular, spheroidal globules varying in size’¹⁴ crowding out red blood cells. Fuller’s 1850 account was of a case of pediatric leukemia. In an article about 35 suspected cases of leukemia,

John Hughes Bennett,¹⁵ a British pathologist at the Royal Infirmary in Edinburgh and a microscopist, included the first known illustrations of blood cells from a leukemic patient.¹¹

Two decades passed before a basic scientific understanding of the mechanisms of leukemia emerged. Ernst Neumann (1834–1918) at the Pathological Institute at Königsberg and Giulio Bizzozero (1846–1901) at the University of Turin independently reported that blood cells originate in the bone marrow^{16–19} and that leukemia is a disease of the bone marrow.²⁰ These groundbreaking discoveries would not be generally accepted until the end of the 19th century; and even then, they were not reflected in treatments for leukemia, which continued to include the use of leeches and arsenic. Notes from a presentation on leukemia to the Medical Society of London reflects this discouraging state of affairs.²¹

There is something wanting in the present plan ... members of the medical profession are continually trying processes for the cure of diseases which have been shown to be useless, and the textbooks continue to recommend medicines which have never done any good.

Apart from this therapeutic stagnation, the work of Neumann and Bizzozero, as well as that of Paul Ehrlich (1854–1915), began to illuminate leukemia’s etiology. Ehrlich invented novel staining methods for the study of the nucleus and cytoplasm of blood cells and classified leukemia as myelogenous or lymphocytic.^{22,23}

Following Röntgen’s discovery of X-rays in 1895, experimental X-ray treatments led to some very short-term suppression of tumors and tumor shrinkage, but with no reported improvement in prognosis. Furthermore, there was no

evidence that these novel radiation therapies had any useful effects on acute leukemias,²⁴ which continued to be 'insidious, rapid, and progressive'²⁵ and rapidly fatal.^{26,27} Between 1926 and 1947, only 3 of 150 adult and pediatric patients with acute leukemias treated at New York's Memorial Hospital survived for a year, and none lived beyond 14 months.²⁸ A review of more than 200 untreated cases of acute pediatric leukemia from this period found that median survival, from the first symptom to death, was 3.9 months.²⁹ Before 1950, childhood leukemia was termed 'acute leukemia' and the sub-classifications of acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) were treated as the same clinical entity — with approximately 4 in 5 being ALL type, the same proportion as today.³⁰

Discovery of the effects of nitrogen mustard on cancer

One line of development of systemic treatments for cancer resulted from classified studies of the effect of nitrogen mustard derivatives on cancer tumors at Yale University, done under the aegis of the Office of Scientific Research and Development (OSRD) of the US Department of Defense.³¹ Autopsies of soldiers killed in the First World War by sulfur mustard gas consistently revealed evidence of leukopenia and lymphoid hypoplasia in the victims. This association was confirmed in December 1943 when a Luftwaffe attack on 17 allied ships at Bari, Italy, aerosolized one hundred tons of sulfur mustard secretly held in a US Liberty ship. A US physician trained in chemical warfare, Lieutenant Colonel Alexander, was flown in from North Africa to investigate cases of acute conjunctivitis and dermatitis, and he found extreme leukopenia in those of the ship's crew who had been exposed.³²

After World War II, findings from the toxic release at Bari and wartime studies by the OSRD and others began to be shared and applied to experimental treatments of cancers.^{33–37} Mustard agents caused brief remissions in several patients with advanced-stage Hodgkin lymphoma and non-Hodgkin lymphoma, and would later be found to effect dramatic remissions in patients with Hodgkin lymphoma.³⁸ Thus despite drug toxicity, the lethality of the diseases, and without knowledge of DNA's role in replicating the

mutant cells that these early treatments were beginning to block,³⁹ a scientific approach to targeting tumor cell growth in humans had been established. However, while these incipient chemical treatments showed promise in temporarily improving the prognoses of patients with lymphomas, there was no evidence that they had an impact in acute leukemias.⁴⁰ The search for treatments for the latter explored alternative strategies.

Folate: initial hopes and early disappointments

Lucy Wills,⁴¹ a British physician working in India in the 1930s, had found that extracts of yeast and liver reduced anemia and leukopenia in pregnant women. She also found that removing this anti-anemic (so-called 'Wills factor') from the diet of monkeys led to a severe reduction in their red and white blood cells.^{42,43} Wills' discovery of what would come to be known as folate or folic acid set off a competitive search among several pharmaceutical research laboratories to isolate and synthesize it.^{44,45} A team led by Yellapragada SubbaRow (1895–1948) at the American Cyanamid Company identified folic acid's structure and was the first to synthesize it,^{46,47} and several early animal studies of folic acid's effects on tumor growth indicated that it might induce tumor regression.^{48,49}

Sidney Farber (then assistant professor of pathology at Harvard Medical School and pathologist-in-chief at the Children's Medical Center Boston), Louis Diamond (assistant professor of pediatrics at Harvard Medical School and a hematologist and physician at the Children's Medical Center), and their three research assistants administered folic acid from SubbaRow's laboratory to 90 patients with late-stage cancers, including acute leukemia. Contrary to predictions based on the preclinical research, they found that folic acid actually *accelerated* the leukemic process to an unprecedented degree, leading to sudden mortality in all patients. Farber concluded that folic acid conjugates should not be used to treat patients with cancer.⁵⁰ Importantly, however, he inferred from the observed 'acceleration phenomenon' that *reducing* folic acid levels might suppress proliferation

of malignant cells and restore normal bone marrow function.

Identifying the effects of antifolates

At Farber's request, SubbaRow's team developed a series of antifolates (folic acid antagonists), including aminopterin,⁵¹ and found that these disturbed the metabolism of leukemic cells in chickens and mice, an effect that could then be reversed by administering folic acid.^{52–54} Encouraged by this evidence, the Farber team began, on 16 December 1947, daily administration of the antifolate aminopterin to a critically ill 8-year-old boy with acute leukemia and a 106°F temperature. Four months later, the disease was in clinical and hematological remission, and the boy was reported to be in 'excellent physical condition.'

Farber and his colleagues went on to study 16 critically ill children with acute leukemia. They monitored each patient carefully, adjusting the daily dose of aminopterin within a range of 0.25 to 1.0 mg, and stopping altogether when crude liver extract failed to mitigate the adverse effects of folic acid depletion. Among the 16 children receiving this novel agent, 10 had unprecedented remissions in the weeks and months following treatment; 2 did not experience remission and 4 died within a few months.

Farber and his team documented the events surrounding 5 of the 10 children exhibiting the 'best results that we have observed'³ and demonstrated for the first time that it was possible to suppress proliferation of malignant cells and to restore normal bone-marrow function in children with acute leukemia. They emphasized that these profound changes were temporary and were accompanied by serious drug-related side effects, including stomatitis, ulceration of the mucous membrane of the mouth, internal hemorrhage, and depletion of the bone marrow leading to aplasia. In a follow-up article published in 1949, Farber offered further evidence of these dramatic effects in a study of 'approximately 60' other children with acute leukemia treated either with aminopterin or with one of two closely related antifolate agents (amethopterin – now known as methotrexate – and amino-an-fol). More than half of these patients experienced important

remissions, similar to those seen in the 10 patients in the first study, with periods of survival well beyond expectation. But Farber remained cautious.⁵⁵

Despite the increasing number of patients in whom temporary remissions have been produced, with survival in some far beyond the usual course of disease, no evidence has been presented which would justify use of the word "cure" of acute leukemia. ... Further research for less toxic related compounds with even greater effectiveness is not only justified by these studies but is imperative. The value of this direction of research in cancer has been established.

Farber's 1948 watershed findings were met initially with strong scepticism.⁵⁶ However, 16 and 23 months after the onset of their disease, two of the five patients described in the 1948 article remained alive with their leukemia 'under control', and this had led to 'widespread use of aminopterin in the treatment of acute leukemia'.⁵⁵

Several other investigators initiated clinical trials of antifolates', also called 'antimetabolites', so named because they inhibit metabolic processes, including cell division. William Dameshek (1900–1969) and his research team at the New England Medical Center at Tufts University reported remissions in 10 out of 32 patients with leukemia who were treated with an antifolate for at least a week; and these included remission in an adult with leukemia. Although Dameshek appreciated the short-term effects of these novel cancer treatments, like Farber, he did not make premature claims that survival would necessarily be affected:

It appears that the folic acid antagonists, although by no means curative in acute leukemia, offer the first ray of hope in the treatment of this disease and may be the precursors of more effective and less toxic drugs. Thus, the results of therapy may be said to represent the beginning of a new era in the therapy of this dread disease. They also lend support to the thesis that in chemotherapy may lie the fate of the ultimate control of cancer and related diseases.⁵⁷

In the decades following Farber's first study with antifolates in children with acute leukemia, chemotherapies would prove to be critical in the

development of effective cancer treatments, and of some cures. To this day a residual compound from Farber's study, methotrexate, which has comparable effectiveness but fewer adverse effects than aminopterin, remains a standard component of the treatment of acute lymphoblastic leukemia, and a key agent in combination therapies for many other cancers.

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