History of leukemia treatment

Four months later, a young German professor at the University of Wurzburg named Rudolf Virchow published a similar case. The patient’s blood was overgrown with white blood cells, forming dense and pulpy pools in her spleen. At autopsy, Virchow found layers of white blood floating above the red. He called the disease weisses Blut – white blood. In 1847, he changed the name to “ leukemia” – from “ leukos”, the Greek word for “ white”.

Virchow was a pathologist in training. He believed that all living things were made of cells, which were the basic units of life. And that cells could grow in only two ways: either by increasing the number of cells, or by increasing its size. He called these two modes hyperplasia and hypertrophy. Looking at cancerous growths through his microscope, Virchow concluded that cancer was hyperplasia in its extreme form.

By the time Virchow died in 1902, a new theory of cancer had slowly come together out of these observations. Cancer an aberrant, uncontrolled cell division creating “ tumors” that would attack and destroy organs and normal tissues. These tumors could also spread (metastasize) to other parts of the body such as lungs and brains.

Leukemia is a malignant overgrown of white cells in the blood. It comes in several forms. It could be chronic and indolent. Or it could be acute and violent. The second version comes in further subtypes, based on the type of white blood cells involved. Cancers of the myeloid cells are called Acute myeloid leukemias (AML); cancer of immature lymphoid cells are called Acute lymphoblastic leukemias; and cancers of the more mature lymphoid

cells are called lymphomas. ALL is the most common leukemia found in children.

Sidney Faber, the third of fourteen children, was born in Buffalo, New York, in 1903. His father, Simon Farber, had immigrated to America from Poland in the late 19th century and worked in an insurance agency. Having completed his advanced training in pathology in the late 1920s, Farber became the first full-time pathologist at the Children's Hospital in Boston. His specialty was pediatric pathology, the study of children's diseases.

Yet Farber was driven by the hunger to treat patients. Sitting in his basement laboratory one day in the summer of 1947, he was inspired to focus his attention to the oldest and most hopeless variants of leukemia – childhood leukemia. The disease had been analyzed, classified, and subdivided meticulously, but with no therapeutic or practical advances.

The package from New York was waiting in the laboratory that December morning. As he pulled out the glass vials of chemicals from the package, he was throwing open a new way of thinking about cancer.

An insatiable monster

Sydney Farber's package of chemicals arrived at a pivotal moment in the history of medicine. In the late 1940s, new miracle drugs appeared at an astonishing rate. But cancer had refused to fall into step in the victories of postwar medicine. It remained a black box. To cure a cancer, doctors had only two options: cutting it out with surgery, or incinerating it with radiation.

Proposals to launch a national response against cancer had ebbed and flowed in America since the early 1900s. By 1937, cancer had magnified in the public eye. In June, a joint Senate-House conference was held to draft legislation to address the issue. On August 5, President Roosevelt signed the National Cancer Institute Act, creating a new entity called the National Cancer Institute (NCI) to coordinate cancer education and research. But World War II had shifted the nation’s priority from cancer research to the war. The promised funds from Congress never materialized, and the NCI languished in neglect. The social outcry about cancer also drifted into silence.

If a cure for leukemia was to be found, Farber reasoned, it would be found within hematology – the study of normal blood. In 1928, a young English physician named Lucy Wills discovered that folic acid, a vitamin-like substance found in fruits and vegetables, could restore the normal genesis of blood in nutrient-deprived patients. Farber wondered whether folic acid could restore the normalcy of blood in children with leukemia. As he injected synthetic folic acid into a cohort of leukemia children, Farber found that folic acid actually accelerated the growth of leukemia rather than stopping it. He stopped the experiment in a hurry.

Farber was intrigued by the response of the leukemia cells to folic acid. intrigued. What if he could find a drug to cut off the supply of folic acid to the cells – an antifolate?

Farber’s supply of folic acid had come from the laboratory of an old friend – a chemist called Yellapragada Subbarao or Yella. Yella was a physician turned

cellular physiologist. Having finished his medical training in India, Yella could not practice medicine in America because he had no license. He started as a night porter at a hospital, switched to a day job as a biochemist, and joined Lederle Lab in 1940.

Enzymes and receptors in cells work by recognizing molecules using their chemical structure. With a slight alteration of the recipe, Yello could create variants of folic acid, and some of the variants could behave like antagonists to folic acid. He sent the first package of antifolates to Farber's lab in the late summer of 1947.

On August 16, 1947, in the town of Dorchester in New England, Robert Sandler, a two-year-old boy was brought to Children's Hospital in Boston. He had been ill with a wax and wane fever for over two weeks, and the condition had worsened. His spleen was enlarged, and his blood sample had thousands of immature lymphoid leukemic blasts. His twin brother, Elliot, was in perfect health.

Farber had received the first package of antifolates from Yella a few weeks before Sandler's arrival. On September 6, 1947, Farber injected Sandler with pteroylaspartic acid or PAA, the first of Yella's antifolates. PAA had little effect. On December 28, Farber received a new version of antifolate – aminopterin. Farber injected the boy with it. The response was remarkable. The white cell count stopped its astronomical ascend, hovered at a plateau, and then dropped. And the leukemic blasts gradually flickered out in the blood and then disappeared. By New Year's Eve, the count had dropped to

one-sixth of its peak value, bottoming out at a near normal level. The cancer hadn’t vanished, but it had temporarily abated.

Sandler’s remission was unprecedented in the history of leukemia. Farber started treating the slow train of children with childhood leukemia arriving at his clinic. An incredible pattern emerged: antifolates could destroy leukemia cells and make them disappear for a while. But the cancer would relapse after a few months of remission, refusing to respond to even the most potent of Yella’s drugs. Robert Sandler died in 1948.

In June 1948, Farber published his study in the New England Journal of Medicine. The paper was received with skepticism, disbelief and outrage. The obliteration of an aggressive cancer using a chemical drug was unprecedented in the history of cancer.

Dyeing and Dying

A systemic disease demands a systemic cure. Could a drug kill existing cancer cells without hurting normal cell tissues? The chemical world is full of poisons. The challenge is to find a selective poison that will eradicate cancer cells without killing the patient.

In 1856, an 18-year-old student in London named William Perkin stumbled into an inexpensive chemical dye that could be made from scratch. Perkin called it aniline mauve. His discovery was a godsend for the textile industry because aniline mauve is easier to produce and store than vegetable dyes. Perkin also discovered that its parent compound could act as a building block for other dyes to produce derivatives with a vast spectrum of vivid colors. In

the mid-1860s, Perkin flooded the textile factories of Europe with a suite of new synthetic dyes in various color.

The German chemist rushed to synthesize their own dyes to muscle their way into the textile industry in Europe. They synthesized not only dyes and solvents, but an entire universe of new molecules such as phenols, bromides, alcohols, and amides, chemicals never encountered in nature.

In 1878, a 24-year-old medical student named Paul Ehrlich did an experiment using chemical dyes to stain animal tissues. He discovered the dyes seemed to be able to differentiate among chemicals hidden inside the cells, staining some and sparing others. In 1882, working with Robert Koch, Ehrlich discovered another new chemical stain that could pick up one class of germs from a mixture of microbes. In the late 1880s, Ehrlich found that certain toxins when injected in animals could produce “ antitoxins,” which could be used to neutralize the toxin with extraordinary specificity.

If biology was a mix-and-match game of chemicals, Ehrlich thought, what if some chemical could differentiate bacterial cells from animal cells so that it could kill the bacteria cells without hurting the animal? So he began with a hunt for anti-microbial chemicals. After testing hundreds of chemicals, he found a dye derivative that can act as an antibiotic drug for mice and rabbits infected with Trypanosoma gondii (a parasite). He called the chemical Trypan Red, after the color of the dye. And in 1910, his laboratory discovered arsphenamine (Salvarsan), the first effective medicinal treatment for syphilis.

His success on Trypan Red and Salvarsan proved that chemicals could be found to cure diseases with specificity. He called these chemicals “ magic bullets” – for their capacity to kill with specificity.

Between 1904 and 1908, he attempted to find an anticancer drug using his vast arsenal of chemicals. None of them worked. What was poison to cancer cells, he found, was also poison to normal cells because cancer cells and normal cells were so similar that made it almost impossible to differentiate.

Ehrlich died in 1915 at age 61. In 1917, two years after his death, Germany used a chemical weapon at the battle of Ypres in Belgium, in the form of chlorine gas. The gas killed two thousand soldiers that night. In 1919, pathologist found the survivors’ bone marrows were all depleted, with the blood-forming cells all dried up.