It was an early afternoon of 1950 in Idaho, a rocky mountain state in the North Western region of the United States. Idaho is a perfect holiday destination with its snow-capped alpine ranges, deep canyons, vast lakes, and rapids. The valley was enveloped with lush green expanse and the warm air filled with a scent of soil and woods felt soothing.

A voice interrupted this quietude. “Hey, Yoda! We are soon going to get some new lambs. I know you are tired. Cheer up, my friend!” Henry turned up the volume of his transistor.

Henry Irigoyen, a man in his early forties, was sitting on his chair, whistling after the famous Basque song. Henry owned the Red Horse Mountain Ranch in Rupert, Idaho. The Irigoyen family had been raising sheep for the past seven decades. Henry’s wait for the ewes to deliver was to be over anytime soon.

In the spring, herds of sheep migrated north from lower valleys to higher mountains for summer pasture. The shepherds had to spend the season at high altitudes, away from their families. Radio was their only amusement during those months of isolation. Consumed by the remoteness, the ranchers cultivated a habit of talking to their pet dogs, who happened to be their sole helpers in the monotonous and tiring task of looking after the sheep. So, keeping up with the Basque culture, Henry often talked to his dog, whom he lovingly called, ‘Yoda’.

It was early May, the lambing season had arrived. The pregnant ewes had been taken to the warm lambing sheds the night before, and the new arrivals were eagerly awaited. Henry’s tranquil musings were disturbed. “It’s a one-eyed-monster!”

As Henry removed his eye-glasses, he saw little Jane running towards him. She gasped, “Uncle, it is a one-eyed monster. I saw it. Aunt Irma would faint if she sees it again.” Henry rushed to the shed. He gazed at the deformed newborn and exclaimed, “What in the world are you?”

A similar problem was being faced by ranchers all over Idaho in the 1950s. The deformed lambs had only one eye in the centre of their forehead in what came to be known as ‘Cyclops’, owing to their resemblance to the one-eyed cannibalistic creatures described in the Greek mythology. The cyclopic lambs often lacked the upper jaw, had an underdeveloped brain, and would die within a few days after birth.

The Idaho lambs exhibited a gamut of malformations and severe developmental defects such as cleft...
palate, a proboscis replacing nose and positioned just above the single eye.

Sheep rearing was the family business of the Idaho ranchers – a means of running their households. Each of the affected animals would cost them about USD 20, a huge economic loss for those times. The ranchers feared that public knowledge of cyclopic births would bring bad name and poor quality to their livestock and ransack their economy. Thus, they chose to be tight-lipped about the monstrous lambs and bore the distressful burden of the mysterious secret within their own community.

No one could decipher the cause of the cyclopic births, but everyone guessed and assumed. There were as many opinions in Idaho as sheep in the ranches. The story of wool-clad monsters became one of the many socio-cultural issues which could be partly explained by science, and largely by irrational, unscientific superstitions such as evil spells, black magic, and devils. Idaho was shrouded with such unreasonable fear of the unknown for years until science arrived close to the town to clear the superstitious fog.

In 1954, the United States Department of Agriculture (USDA) established the Poisonous Plant Research Laboratory (PPRL) at Logan, Utah, the neighbouring state of Idaho. The Idaho ranchers came to know about PPRL one fine evening in the year 1955.

Irma Irigoyen was preparing supper while Henry pondered over the cause of the one-eyed sheep with fellow ranchers at the dining table. The cyclopic births would be the indisputable topic of dinner gatherings in Idaho households.

“I told you to knock on wood of four pine trees and chant, but you did not listen.” Irma was advocating a new ‘magical charm’. Henry cut her short. “Don’t start that again Irma. I did that and it just does not work.”

“But then you broke my mirror, last Sunday.” Irma’s irrational reasoning to describe the incidence of cyclopic lambs would not stop.

“Oh! Stop that Irma. We tried all those things and still having those births.”

“Superstitions,” said Jonathan, one among the educated folks of the rancher community. Suddenly, all eyes glued on to his face. Jonathan continued, “I went to Utah with schoolmates last summer and visited a few scientists at the PPRL, a huge building that houses several laboratories. The scientists at PPRL do research and study of poisonous plants that animals may eat.”

A brief thoughtful pause seemed to consume every atom of air in the room. Henry snapped, “We’ve been feeding the same fodder for the past seventy years. You can’t question our food.”

“The sheep are not infants,” uncle Henry, Jonathan explained. “They don’t always feed on what you give them, rather they have a mouth, four feet, and a hungry stomach. Moreover, you must not forget that the sheep are not always in the ranches.”

“What is the probability that it could be genetic?” questioned Mr Gregory.

“I think there cannot be a defective gene in all of those sheep. I mean they are from different herds, not always related by lineage,” Jonathan contradicted Mr Gregory with a good argument.

“So, you say that it is a poisonous plant,” Henry continued after a brief silence.

“I am not sure, but it is a possibility. I guess scientists can test this likelihood for us,” Jonathan enveloped his words with a hopeful persuasion.

The dinner conversation led to the emergence of a fresh and hopeful window of investigation and triggered quick actions among the Idaho ranchers. A team of researchers from PPRL, including Dr Lynn F. James set out to solve this problem, without the faintest notion that the effort would last for the next eleven years.

The scientists began a systematic study of the one-eyed lambs. The first obvious step was to rule out the genetic disposition of the defects. Ewes that had given birth to the cyclopic lambs were bred and to their surprise none of the developmental imperfections were observed in the progeny.

Local grasses and plants from the area were collected and fed to rats, but scientists could not recapitulate similar deformities. Dr James and his team domesticated themselves with the sheep in the ranches. They spent three summers in Idaho studying water, soil minerals and plants for potential teratogenic properties. The team would follow the sheep, much to their annoyance, to observe their behaviour.

A PPRL employee got the final clue during a candid conversation with one of the shepherds, who revealed
that the sheep would get sick after they grazed on *Veratrum californicum*, Western False Hellebore or corn lily. Some ‘fugitive’ ewes would often escape to higher altitudes (6,000-10,000 feet) during their yearly pilgrimage to the mountains. There the ewes would munch down the fleshy leaves of corn lily and would come back silently to their herds.

Not wasting an iota of time, experiments were initiated and the sheep were fed on corn lily. The feeding experiments revealed the poisonous nature of corn lily as the sheep manifested physiological responses of toxin ingestion, and in severe cases death.

One of the experiments, wherein corn lily feeding was done in a controlled manner, resulted in the birth of a cyclopic lamb at PPRL in 1959. The PPRL scientists had finally figured out the evasive culprit.

The ranchers had a celebration calling in. Jonathan was invited as a special guest for dinner at the Irigoyen’s. Henry’s radio played songs at its highest pitch. Yoda, the dog was happy for he would not have to hear his master’s gloomy musings anymore. The shepherds could control the cyclopic events in the lambs by curtailing the access of pregnant ewes to corn lily. For the ranchers, the case of Idaho had closed.

However, for the scientists, the other layers of the problem were yet to be solved. The researchers took about 48 pregnant ewes for a picnic to munch on *V. californicum* in Muldoon Canyon in the Challis National Forest. The ewes grazed on corn lily for varied duration and different time points during pregnancy. A few sheep of the herd gave birth to cyclopic lambs with other deformities.

The same ewes, when rebred and not fed with corn lily, would produce normal lambs. By the year 1965, the scientists could decipher that cyclopia would occur only when the ewes ingested the plant at around 14th or 15th day of gestation. A few more years of laboratory adventures led to the discovery of the real active chemical ingredient in the plant. In 1968, the chemical responsible for cyclopic deformities was identified and christened as ‘Cyclopamine’.

The “why” and “who” part of the problem was solved, but the “how” part was still a veiled secret. Nevertheless, the Idaho case closed at PPRL without the remotest idea that cyclopamine would resurface in an identical context years later.

Let us move towards the east in the year 1976. Among many students sitting in the library of Goschen college, Indiana, one student was particularly hooked to the New Yorker Times magazine. The magazine published a serialized version of Horace Freeland Judson’s book, *The Eighth Day of Creation*. The book recounts the story of the birth and early development of molecular biology. Who knew that this student, Philip A. Beachy, would become a renowned molecular biologist and the elucidator of the hedgehog signalling pathway.

Beachy wanted to uncover the molecular mechanisms behind the development of multicellular organisms. How does the apparently lifeless cluster of cells give birth to live in a well-organized body? The fruit fly, *Drosophila melanogaster* was his model organism of choice to answer some of these questions while he worked as a researcher at John Hopkins University.

Beachy studied the function of *Drosophila* ‘hedgehog’ gene. The early *Drosophila* embryos which lacked the hedgehog gene were found to be covered with spine-like structures resembling the skin of a hedgehog. Thus, the gene was named *hedgehog* (*hh*). Hh was identified as a gene with an important function in laying out body plan in animals. It initiates a signalling action instructing the embryo cells to grow in...
a symmetrical manner, and is involved in differentiation of the central nervous system, eyes, skin, muscles, cartilage, and other organs during early body plan organization. Hh gene is present in mouse and humans and is called Sonic Hedgehog (Shh).

To study the function of Hh gene Beachy followed a simple approach – he prevented the gene from working and noted the changes. Beachy used mice to mutate the Hh gene and surprisingly ended up creating embryos similar to the deformed Idaho sheep with cyclopic eyes. Defects in Shh gene induce cyclopic phenotypes in humans as well.

By a matter of fate, in 1996, Beachy stumbled upon a photograph in the textbook Developmental Biology. It was the photograph of a cycloptic lamb of Idaho. By 1998, Beachy strung the loose ends together – cyclopamine produced the same effects as produced by a mutant Hh gene. Beachy demonstrated the action of cyclopamine as a chemical inhibitor of the Hh signalling pathway. The ‘How’ part of the Idaho mystery was finally unveiled. However, the story doesn’t end here nor does the science.

Let us come, 13,595 km east of Idaho, to present-day India. An excerpt from the Times of India had a different story to tell: “Based on the data between 2010 and 2012, it is suggested that at some point during their lifetime approximately 39.6 percent of the population including male and female will be diagnosed with cancer. In India, it is estimated that 14.5 lakh people are living with the disease, with over 7 lakh new cases being registered every year and 5,56,400 deaths are going to be cancer-related.” Indeed, cancer has emerged as a ‘modern-day plague’, and its occurrence among the human population is approaching epidemic proportions.

The discovery of cyclopamine as an inhibitor of Hh pathway proved to be path-breaking for the reason that Hh signalling gets activated in various kinds of cancers including those affecting skin, brain, glia, prostate, pancreas, etc. Scientists reasoned that cyclopamine could be used as an anticancer agent.

Beachy along with another scientist Berman demonstrated that cyclopamine could reduce the tumour size in mouse brain cancer model. A few years of medicinal, chemical and pharmacological research went into developing derivatives of cyclopamine and testing it in animal models such as sheep and mouse. Cyclopamine has been shown to be effective in inhibiting Hh signalling in mouse models of several types of cancer. Topical skin creams containing cyclopamine have been administered to skin cancer patients.

Cyclopamine has certain limitations for human cancers affecting internal organs and tissues. Solubility in water and normal saline is an issue. Cyclopamine is not very stable under acidic conditions of the gastrointestinal tract. However, several semi-synthetic derivatives and salts of cyclopamine have shown promise to overcome these limitations, for example, 3-keto-N-(aminoethyl-aminocaproyl-di-hydrocinnamoyl) cyclopamine, 2 (KAAD-cyclopamine), exhibit better anti-cancer potency. IPI-92, a compound with a number of synthetic modifications to cyclopamine exhibits increased stability and potency. It has been used in the treatment of brain, lung and pancreatic cancer. Cyclopamine, in combination with other anticancer drugs, is being tested as clinical trials on humans with metastatic pancreatic cancer.

Cyclopamine was the first anti-cancer small molecule discovered by inhibiting the tumour-inducing Hh pathway. It has served as a prototype molecule around which new anti-cancer chemotherapeutic agents are being developed. From a pharmacological perspective, research on cyclopamine gave conceptual and technical insights on the modulation and control of Hh pathway in cancer tissues. From a biological perspective, it revealed that certain genes that control embryonic growth may contribute to cancer later on in life.

The story of cyclopamine emphasises the interdisciplinary and nonlinear approach to problem-solving. It is a story where the boundaries between science and society interweave, where common people and scientists join hands and seek answers to nature’s mysteries.

The case of the mysterious lambs of Idaho initiated a research in agricultural sciences, which led to the discovery of corn lily as a poisonous plant. This was followed by chemical research on the teratogenic agent present in corn lily, later named as cyclopamine. This study was further interlinked with Beachy’s research (Hh gene) in developmental biology and consequently to the possibility of cyclopamine derived anti-cancer drugs.

Renowned playwright and activist, Bernard Shaw aptly said, “Science never solves a problem without creating ten more.” The case of Idaho exemplifies this in entirety.

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