THE STORY OF CANCER: DOWN THE RABBIT-HOLE*

"None answer's this; but after Silence spake
A Vessel of a more Ungainly make:
They sneer at me for leaning all awry
What? did the Hand then of the Potter shake? "
(Fritzgerald E. Rubáiyát of Omar Khayyám (Oxford World's Classics), Oxford University Press, 2009)

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From the earliest of times, human beings have lived in awe of the forces of Nature, and agonised over the (often) cruel edicts of Destiny and Fate. In the Quatrain quoted above, the great Muslim poet and mathematician Omar Khayyam, most eloquently, refers to this very conundrum. Why is there so much sorrow, pain, and (from a bio-medical perspective) disease, in this World of ours?

The utterance: "What? did the Hand then of the Potter shake?" from the 'lips' of a Pot of Clay, sounds almost blasphemous. However, should we not forgive this unfortunate "Vessel of a more Ungainly Make" (abnormal / deformed / damaged), for its expression of this (apparently) sacrilegious sentiment? In the same vein, can a human being afflicted by some terrible disease, not cry out in anguish at the (apparent) injustice of the Divine Hand, in an attempt to find some semblance of meaning in apparent Chaos?

At this stage, we have to acknowledge, that the Scientific Method is poorly equipped to answer these fundamental questions. Such grand matters, which have been of ultimate concern to humanity – Ethics, Morality, the Soul, Spirituality, Sacredness – will always be the rightful realm of Religious Faith (Iman). Amen to that!

However, to my mind, Khayyam's symbolism, reflects most acutely the most difficult and complex problem - confronting physicians/surgeons in general and oncologists/pathologists in particular – of neoplastic disease (i.e. cancer), which truly represents the greatest challenge facing us!

"Cancer", the most aptly described "Emperor of all Maladies", has been the scourge of Mankind since records began. The earliest written description of human cancer appeared in ancient Egyptian manuscripts ("papyri") discovered in the 19th century by Edwin Smith and George Ebers, written between 1500 & 1600 BCE, most likely referring to much more ancient records. It is believed that Imhotep, the mythical physician of a bygone age (c. 2650–2600 BCE) may well have recorded the first reference to breast cancer in one of these archaic documents. *Carroll L. Alice's Adventures in Wonderland. Gramercy Books, NY, 1995.

After the ancient Egyptian civilisation declined, Greek medicine became preeminent, especially with "Great" Hip-pocrates of Kos (460-c.360BCE), whose approach to diagnosing diseases was based upon careful observations of his patients' signs and symptoms. Later on, Galen (c.129–c. 216) was Hippocrates' most prominent successor, and propelled his legacy for nearly 15 centuries. Galen's prolific writings include 300 titles of which only about half have survived wholly or in part, many destroyed in the fire of the Temple of Peace (CE 191).

With the collapse of Greco-Roman civilization, after the fall of Rome in CE 476, medical knowledge in the West-ern Roman Empire stagnated and many ancient medical writings were lost. Latin translations were not readily available and few scholars could read Greek. Yet, Greek medical tradition remained

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alive and well in the Eastern Roman (Byzantine) Empire.

Islamic interest in Greek science and medicine during the Abbasid period led to translations of Galen's work into Arabic, many of them by Syrian scholars. It has been written, that a critical role was played by one Ja'far Ibn Barmak (minister of the Caliph of Bagdad), in the adoption of Greek thought by the Muslims (Arabs).

Islamic physician scholars and medical writers became preeminent in the early middle ages. The most illustri-ous and influential in that era being:

• Abu Bakr Muhammad Ibn Sazariya Razi, also known as Rhazes (865?-925?),

• Abu Ali al-Husayn ibn Abd Allah Ibn Sina, known as Avicenna (980–103),

• Abu-Marwan Abd al-Malik ibn Zuhr or Avenzoar (1094–1 162) and

• Ala-al-din abu Al-Hassan Ali ibn Abi-Hazm al-Qarshi al-Dimashqi or Ibn Al-Nafis (1213–1288)

The Anatomy Canon of Avicenna, a manuscript discovered in the Prussian State Library of Berlin, is one of the marvels of Islamic medicine. In fact Ibn Sina was the first scientist to understand the function of coronary circu-lation.

It was Avenzoar who first described oesophageal and gastric cancer in his magnificent book Kitab al-Taysir fil-Mudawat wal-Tadbir (Practical Manual of Treatments and Diets), and proposed feeding enemas to keep alive pa-tients with stomach cancer. Like Hippocrates, he insisted that prospective (student) surgeons should receive hands-on training, before being allowed to operate on his own. By the end of the fourteenth century, Avenzoar became well known in university circles at Padua, Bologna, and Montpellier where he was considered one of the greatest physicians of all time. Successive publication s of his Kitab al-Taysir and of translations ensured his influence well into the seventeenth century.

Sadly, the Mongol destruction of capital of the Abbasid Caliphate, Baghdad in 1258, and the fall of Islamic Spain (Granada) marked the decline of Islamic Medicine. On reflection, it almost seems as if a 'perfect storm' of unrelated tragic events, conspired against the Glory of the Muslim world.

In Europe during the Middle-Dark Ages (500-1400 CE), there was a proliferation of Monasteries, which become repositories of Arab-Greek medicine. An important figure of this era was Constantine Africanus (a Tunisian, Tuni-sia was known Ifriqiya at that time), whose translations and annotations of Arabic (and Greek) medical texts made famous the Studium Hospitium (hospice/hospital) at Salerno (Italy). This was the beginning of an influential and enduring phase of advances in knowledge, with medical schools being established at Montpellier (1150), Bologna (1158), and Paris (1208). Later on during the (so-called) European Renaissance, Andreas Vessalius (1514–1564), Ambroise Paré (1510–1590) and Gabriele Fallopius (1523–1562), amongst others, were significant figures, in the development of "scientific" medicine of that era.

However, even in those early days, cancer was known as an incurable, deadly condition. Francois Le Dran (1685–1770), one of the best surgeons of his time, postulated that cancer developed locally but spread through lymphatics becoming inoperable and fatal. Joseph Recamier (1774–1852) first coined the term "metastasis" in 1829. Giovanni Battista Morgagni (1682–1771) wrote, what is considered by many to be the first pathology text-book: "De Sedibus et Causis Morborum per Anatomen Indigatis" (On the Seats and Causes of Diseases as In-vestigated by Anatomy), which defined a new era in the study of tumours (cancer). In 1713, Bernardino Ramazzini (1633–1714) of Padua, made the important observation of a virtual absence of cervical cancer, but higher inci-dence of breast cancer, in Nuns related to married women – an early astute observation of virus- and hormone-related carcinogenesis.

Further on, an English Botanist John Hill (?1716-1775) warned of the dangers to health of Tobacco. Percivall Pott (1714–1788) noted the increased incidence of scrotum cancer in chimney sweeps – an important early observa-tion of chemical carcinogenesis. During that period, several other important clinical associations were noted, in-cluding recurrences distal to the original cancer, multiple cancers in a single individual, and families with a high incidence of cancer (by Jacques Mathieu Delpech (1772 –1835), Gaspard Laurent Bayle (1774–1816), Pierre Paul Broca (1824– 1880), James Paget (1814–1899), and Carl von Rokitansky (1804–1878)).

In 1839 Johannes Muller (1801–1858) published "On the fine structure and forms of morbid tumors" which remains a seminal publication in tumour pathology. Rudolf Virchow (1821–1902), is credited with being the 'Father' of Cellular pathology - the phrase "omnis cellula e cellula" (every cell originates from another existing cell like it) is attributed to Virchow. However, in his three-volume work, Die Krankhaften Geschwulte, Virchow had originally postulated that carcinomas originated from connective tissue cells and not from epithelium. Interestingly, it was Robert Remak (1815–1865), who had first discovered that, the origin of cells was by the division of pre-existing cells. Theodor Boveri (1862–1915) first proposed a role for somatic mutations in cancer development based on his observations in sea urchins.

At this stage it interesting to note that, even though the currently accepted concept of carcinogenesis posits a 'cellular origin' to tumours, valid alternative models have been proposed which assign 'tissue' the fundamental focus in malignancy – somewhat reminiscent of Virchow's original concepts!

Interest in a possible bacterial or parasitic link to cancer was first raised in the 17th & 18th centuries. Between the 1880s and the 1920s, there was a huge effort to find cancer-causing micro-organisms. In fact, Andreas Grib Fibiger (1867–1928) was awarded the 1926 Nobel Prize in Physiology or Medicine for his discovery of the 'cancer causing nematode', Spiroptera carcinoma. Although such early studies were later found to be inaccurate, the ba-sic concepts of 'infectious' aetiology of cancer, have in fact, found support in at least some cases. Peyton Rous (1879–1970) demonstrated the viral origin of cancer in chickens and was awarded the 1966 Nobel Prize for Physiology or Medicine for this discovery. Today, the association of Helicobacter pylori and gastric cancer is well established. Also, the International Agency for Research on Cancer (IARC) has classified the following viruses as group 1 human carcinogens: Epstein-Barr virus (EBV), hepatitis B virus (HBV), hepatitis C virus (HCV), Kaposi's sarcoma herpes virus (KSHV), human immunodeficiency virus, type-1 (HIV-1), human T cell lymphotrophic virus, type-1 (HTLV-1), and human papillomavirus (HPV).

At this stage is worth mentioning, that the original hypothesis of bacteriological basis of cancer left a more pervasive and counterproductive parallel with infectious diseases: that cancer cells, like bacteria, are foreign invaders that must be eradicated at all costs!

Thus, at beginning of the 20th century, there was much controversy regarding the mechanism of carcinogenesis. In 1903, an editorial in the British Medical Journal stated: ''…. few things, even in medicine, have ever been so tangled as the views which are held by different people on the origin and cause of cancer'' (Plimmer HG. Chair of Comparative Pathology, Imperial College of Science and Technology, 1917-1918; Fellow of the Royal Society, 1910; President of the Royal Microscopical Society, 1911-1912).

During the 1940s onwards, researchers continued the search for the cause of cancer with much urgency. One important development, was the proposal of the theory chemical carcinogenesis, in three stages: initiation, promotion, and latency. Chemical substances such as oils, tar, petroleum, rubber products, were conclusively shown to be carcinogens in

experimental animals. It was also discovered that laboratory animals on a diet of Brazilian groundnuts developed liver tumours. Aflatoxin, the responsible chemical agent, was identified and traced to contamination of the nuts by a fungus, Aspergillus flavus.

In the 1960s, nitrosamines, and a number of other compounds were added to the long list of organ-specific car-cinogens in experimental animals. These discoveries were followed by experimental confirmation that exogenous oestrogen is capable of inducing mammary carcinoma in several different species of laboratory animals.

The 1953 discovery of the three-dimensional structure of DNA by Watson & Crick (aided by Rosalyn Franklin's X-ray diffraction studies), was crucial in establishing the concept of DNA damage as the cause of cancer. However, it was a German surgeon and cancer researcher, Karl-Heinrich Bauer who in 1928 (by observing mutations in plants and animals), had first proposed idea that cancers were likely caused by mutations.

At this point, we may recall that it was the German biologist Theodore Boveri, who in 1914 first proposed that tumours arise from chromosomal abnormalities. The (somatic) 'mutation theory' (SMT) of cancer, evolved slowly during early years of the last century (1918-1930). Over the ensuing decades, this concept became increasingly accepted and became the basis of intense biomedical research, with innumerable publications in the literature. In short, the SMT posits that cancer is the result of progressive accumulation of random mutations and increased deregulation of key molecular pathways.

For clarity, it may be useful to the revisit the 'genetic' basis of separating different types of human cancers: First, there are tumours that are inherited through the germline of the carriers - they represent about 5% of the total in-cidence of human cancers. There is consensus about the mutational origin of these inherited cancers. Second, are "sporadic" tumours that represent 95% of all clinical cancers, putatively the result of a variety of chemical, physical and biological (environmental) agents. It is these 'sporadic' cancers which have been the target of the long 'War on Cancer' declared by US President Richard Nixon, way back in 1971.

Over the past two decades, there has been an explosive growth in scientific knowledge of the bio-molecular fac-tors involved in carcinogenesis. The enormous development of genetics, biochemistry and molecular biology during the twentieth century made possible the emergence of the big scientific-technological revolution of recombinant DNA. In turn, this made possible new and accelerated advancements associated with (so-called) ''Omics'' and bioinformatics, allowing for high throughput and high content analysis of biological data.

On the other hand, all this new and sophisticated technology for the massive acquisition of biological data ap-pears to have widened the gap between the 'deluge' of biological data available and the (very) limited amount of actual new (actionable) knowledge. At the turn of the millennium, biologists faced for the first time the challenge of what to do with these new data, which are being massively acquired at a rate much faster than that required for their processing?

Thus, as we approach 2015, the Story of Cancer continues to unfold, with even more intricate plots and unex-pected twists. In fact, the current leaders of the field appear to be as confused as anyone else. One of the 'Godfathers' of the current SMT 'paradigm' of cancer biology-oncology, Dr Robert Weinberg (co-author of the highly influential "Hallmarks of Cancer" paper), wrote a leading edge essay in the prestigious scientific journal CELL in March this year (Cell. 2014; 157: 267–271). The article makes difficult reading, to quote:

"…… how and why a cancer cell behaves as it does is still far beyond our reach

…… the data that we now generate overwhelm our abilities of interpretation

…... we lack the conceptual paradigms and computational strategies for dealing with this complexity ……. (etc) ….. ”

Thus, as we cautiously journey down the Rabbit-hole, in search of that elusive White Rabbit (the cure for cancer) - it appears that this long, winding, tunnel has lead us to a cul-de-sac, a dead end. What next? Should we re-trace our path back? Or attempt an alternative route? Or simply give up?

It appears that, the resolution to the current impasse in the understanding of malignant tumours (cancer), may lie in an honest revaluation of the technique we have used (‘path we have followed’), for the past many, many years, in our attempts to find an answer to this most difficult problem.

The Reductionist Method of dissecting biological systems into their constituent parts, has been effective in ex-plaining the chemical basis of numerous living processes. However, it is becoming increasingly obvious that this approach has reached its limits – especially with reference to the major challenges we face in medicine today: chronic (autoimmune / degenerative) diseases and cancer.

How can we catch (or tame) the White Rabbit?*

But that my friends, is a Story for another day ……..

*Carroll L. Alice's Adventures in Wonderland. Gramercy Books, NY, 1995.

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