

The History and Mystery of Breast Cancer

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By

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***La Fornarina* does not have breast cancer**

Front cover *Raphael's La Fornarina (1520), oil on panel – 85 X 60 cm. Galleria Nazionale d'Arte Antica in Palazzo Barberini.*

Margherita, Raphael's model, is pointing to her heart as a token of her love for the artist. The hand or finger resting on the left breast is a classic pose from the times of antiquity much favoured during the Southern Renaissance. Apart from the intrinsic beauty of the pose, there is a significant iconology either by indicating the organ of lactation (mother love, nature's bounty) or the underlying heart (anguish, love). Further evidence is provided by the "love band" inscribed with the name Raphael on the left upper arm. The closeness of their relationship is also supported by the evidence that *La Fornarina's* portrait was found in Raphael's studio after his death. In 16th Century Italy the ideal female form demonstrated pyramidal shaped breasts set very high on the thorax. It has been suggested that a puckering of the breast just above the left index finger is evidence of a cancer deep to the skin. However, a simple experiment will demonstrate that if a woman applies gentle pressure with the index finger, just below the left nipple, a dimple like this will appear. In my opinion *La Fornarina* does not have breast cancer, she is simply in love with Raphael.

This book is dedicated to my daughters Katie & Suzanne
and all the members of the Latte Lounge

*Leave her to heaven and to those thorns that in her bosom lodge
To prick and sting her.*

William Shakespeare
Hamlet Act IV Scene V

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The Beauty of Nature and the Nature of Beauty:

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אֵשֶׁת חַיִּיל - Eshet Chayil Me Yimtzah?

Who can find a woman of valour? Her value is far beyond that of rubies. The heart of her husband trusts in her and he lacks nothing good. She does him good and not evil all the days of her life. She looks for wool and flax and sets her hand to them willingly. She is like a merchant's ships, bringing food from afar. She arises while it is still night, and provides food to her household and a portion to her maidens.

My mother, Mary Baum, died on my birthday (May 31st), 1974. A quotation from Proverbs 31:10-31 (See above) is inscribed on her headstone. My mother was only 65 at the time of her death from metastatic breast cancer. She was indeed a woman of valour of value beyond rubies. I was the middle child of her brood of 5. We grew up in the East End of London during the blitz and lived through the period of extreme austerity in the post war years. Two refugees from Germany added to her burden. She arose while it was still night to provide food for her household. That entailed lighting a coke burning stove in the depths of winter that included the deep freeze of 1947. She manufactured the most delicious meals out of the least promising ingredients and made her own bread, noodles and cottage cheese. I remember watching her labouring away in an out-house where our dirty clothes and sheets were boiled in a giant cauldron. I thought it was a game when she let me wind the wet sheets through the mangle but I was too weak to lift the two heavy irons that heated up in tandem on the stove.

My father was away a lot struggling to make a living as a traveling salesman and taking his turn in the Home Guard. My two older brothers tried their best to help in between their studies and my youngest brother was but a babe in arms as the bombs fell from passing Luftwaffe squadrons. My youngest sibling, Linda, was born after we'd moved to Birmingham but were still suffering from austerity and dependent on food and clothe coupons because of the rationing. Consequently, another lasting memory was of my mother darning socks with a mushroom shaped gadget in her hand to expose the hole to her needle and thread.

We were an orthodox Jewish family that on the one hand provided community support but on the other hand demanded of her to cook exceptionally wonderful dinners for the Sabbath and the High Holy Days. The smell of her slowly cooking *cholent* wafts into my study as I type these words and the taste and texture of her cheesecake has me salivating in its memory.

I have no recall of her relaxing or doing anything self-indulgent, there simply wasn't the time. Yet she was always smartly turned out and I never saw her without make up or with her hair in a mess. Her hair was always worn as a shiny black chignon with a complex array of combs and chopsticks holding it in place. She prided herself on her hair and claimed she could sit on it when let down. Sadly, she never let her hair down whilst I was around. I have little doubt she neglected herself and by the time her breast cancer was diagnosed it was inoperable and had spread throughout her skeleton. The chemotherapy regimen she endured provided no relief but only added alopecia to her suffering. She died in agony denied the morphine she required because of the putative risk of shortening her life by suppressing her respiration. (We now know this is a false assumption).

My little sister Linda, developed breast cancer at the age of 45 about 25 years ago. She was responsible for four daughters, a lawyer for a husband and a large ginger dog. She was also responsible for the department of speech and language therapy in her local NHS health district. She was well-aware of the significance of a lump in the breast but was fortunate to have direct access to the best specialist services in the land. By then I was Professor of Surgery at the Royal Marsden Hospital and the Institute of Cancer research. One telephone call from me and the next day she saw a breast cancer surgeon I trusted. Within 48 hours, tests were completed and diagnosis confirmed. A week later she had breast conserving surgery, three weeks later she started a course of post-operative radiotherapy and then embarked on a 5-year course of tamoxifen 20mg daily. She retired from her responsibilities within the NHS last year at the age of 70.

I have two daughters in their late 40s, Katie & Suzanne. Between them they share 7 children, two insanely energetic dogs and two workaholic husbands. In synchrony, their careers have just taken off leaving little time to take care of themselves but at least they have me at hand, an e-mail, text or live phone-call away. Their health concerns as peri-menopausal women are taken care of by my network of old friends and colleagues but I still worry about them and our family history of breast cancer.

These three generations of my family represent the most important demographic sub-group in modern society; women aged 40-65. They are the ones bringing up our children and worrying about their aging parents. “The filling between two slices of bread”. In addition, in the age of sexual equality they are at the peak of their professions. Many of my young protégés were women who were appointed as consultant surgeons or Professors during this passage of their lives. Such women are also entering their peri-menopausal years and going on to suffer the consequences of the menopause in the age bracket 45-55. As well as the climacteric syndrome, these women also must cope with feelings of low self-esteem and depression. Because of the heavy burden they must carry, they are often guilty of self-neglect and their health needs ignored. Breast cancer is also a threat to this age group. I spent most of my professional career looking after such women and my love and respect for them has inspired me to write this book.

These days it is considered good form for doctors to involve their patients in the decision-making process, but most merely pay lip service to this ideal. I sympathise with both sides of this dialogue because the subject is so difficult to understand. I am reminded of graffiti I once spotted on a wall driving into Belfast from the airport on my way to examine the students for their finals. *“Anyone who can explain the Irish situation doesn’t understand it.”* Breast cancer and its treatment is a terribly complex problem that involves all the complexities of the human body, the anatomical and microscopic anatomy of the breast, the endocrine (hormones) system, bone metabolism as well as the nature of malignant transformation. I have studied this subject for 50 years and still have many uncertainties. I also believe that there is an ethical obligation to share our uncertainties with our patients when we are looking for informed consent before our invasive procedures.

Although the core material relates to breast cancer the book attempts to go way beyond this. You can’t begin to understand the problem unless you have a grasp of the beautiful symmetries of the human body and its organs in health. You can’t begin to make progress with breast cancer without learning about the long tragic history of our mistakes. *“Those who fail to learn from the mistakes of their predecessors are destined to repeat them.”* You can’t understand how we made such mistakes and how we can avoid them in the future without a passing knowledge of scientific philosophy, statistics and clinical trials. You can’t understand how much progress we have made already and the potential for future progress unless you understand clinical trials and are willing to volunteer to take part. The

patient must be aware of the delicate trade-offs between improving length of life at the expense of quality of life (QOL). That's why I also include a chapter on measuring QOL and patient reported outcomes (PROMS). The last section of the book is dedicated to my concern for the totality of women's health.

As I write this my country is struggling to understand the consequences of the Brexit vote and a majority now wish they had a second chance to vote. That is the consequence of making important decisions without adequate information. A wrong decision on Brexit may affect our wealth but a wrong decision about breast cancer might affect our health or even make a difference between life and death.

I have been privileged to enjoy more than one career in my long and busy life.

I qualified as a doctor in 1960 and was appointed to my first chair of surgery in 1980 at Kings College London and went on to be appointed Professor of surgery at the Institute of Cancer research in 1990 and then to a chair of surgery at University College London (UCL) in 1997. I retired from my clinical work as a surgeon at the age of 67 but was kept on as a part time non-clinical post with the title of visiting Professor in Medical Humanities at UCL. In that role, I helped set up a new curriculum in the teaching of the humanities to medical students. This involved teaching scientific philosophy, moral philosophy, the psycho-social impact of disease, communication skills, narrative based medicine, the history of medicine, and the role of the performing arts and the visual arts in the practice of medicine. As someone who has submitted himself to a course in communication skills himself and then passed on this knowledge, I like to think that I can communicate with lay people in the way I used to teach my first-year medical students.

In this book, I want to equip women with the knowledge to understand the workings of the human body, the meaning of malignant transformation of healthy tissue, the nature of the scientific process and the evaluation of new data as it emerges. This might sound like an ordeal, equivalent to understanding trade tariffs, hard and soft borders and different levels of economic union, but my intent is to make it accessible, entertaining and of immediate relevance.

The book is divided up into four sections.

- The beauty of nature and the nature of beauty
- How do we know what we know?
- The history of breast cancer
- My hopes for the future

The first section will be an introduction to human biology and the structural beauty of the human biology at both the macroscopic and microscopic level. I want you to share my awe and wonder at the beautiful creation of the evolutionary process that is *homo sapiens*. The loss of this beautiful organisation helps us understand what happens when things go wrong and leads to oncogenesis (malignant transformation)

The second section is an introduction to scientific philosophy and how this relates to the acquisition of knowledge. In simple terms this will cover the elaboration of a hypothesis and its testing through the process of falsification. (*Epistemology* in the scholarly description of the study of the growth of knowledge).

The clinical trial is then described as the application of the scientific method for the testing of new treatments. Along with this I will describe some simple statistical tests that help us analyse the data. You don't have to have an A level in mathematics to understand this section because it's the concepts that are important not the sums. In any case, we have computers these days to solve complex mathematical problems.

The third section of the book will trace the history of breast cancer and its treatment from the time of the ancient Egyptians to the present day. This will be more than a linear narrative but an exposition on how conceptual models of the disease have evolved over time. Each conceptual model has determined a therapeutic response. Each of these eras has been associated with tragic consequences as futile attempts to cure breast cancer have simply added to the sum-total of human suffering. The history in the current era ends on an optimistic note as I trace the progress over the last 40 years that has contributed to significant improvements in length of life and quality of life for women diagnosed with the disease.

The last chapters look to the future and explain the limitations of our current conceptual model of breast cancer and the outlying observations that might help with a more refined understanding of the disease. The failure of the screening experiment is described in detail so that we can once again learn from the errors of the past. The new conceptual model

that is emerging is very exciting as it can account for the successes of the past yet point the way the next therapeutic revolution.

Our obsessive ruminations about the threat of breast cancer means that few in the lay public know that this disease has slipped down the league to 7th causes of death for women. Yet treatments for breast cancer might increase the risk of death from cardio-vascular disease whilst on the other hand denying women in this age group HRT for the unjustified fear of breast cancer, can impair their QOL, cognitive function and bone mineral density. The totality of women's health and expectation of life must always trump the single-issue fanatics who only view women as the sum of their two breasts. Breast cancer cannot be considered in isolation but as only one issue in a complex network involving the totality of wellbeing. Women must play their part in this and not continue as passive pawns in this great endeavour.

On June, the 15th 2018, The Academy of Medical Royal Colleges issued a new directive with the catchy headline, "BRAN is good for your health". BRAN is not breakfast cereal but stands for, Benefits, Risks and Alternatives to a treatment, and what would happen if they did Nothing. This directive is of historical importance as it effectively redresses the power imbalance in the doctor-patient relationship. There is now a mandatory responsibility for doctors to describe the potential benefits or harms of treatment they recommend together with drawing attention to other options available including the option of doing nothing.

Yet surprisingly this is not a new idea, it was advocated as long ago in a letter to the Lancet by Morgan and Blamey in 1984.

Women must not be passive in their search for good health. Women must educate themselves and then play the part as equal partners in the doctor patient relationship. With this revolution, there comes a responsibility. If you have a duty of care for yourself you also have a duty of care for your sisters and daughters. Understanding breast cancer and improving its treatment cannot be left to laboratory scientists experimenting on mice. It is up to the clinical scientist running clinical trials in partnership with their patients to advance the subject.

PART ONE:

**THE BEAUTY OF NATURE AND
THE NATURE OF BEAUTY**

CHAPTER ONE

THE BEAUTY OF NATURE AND THE NATURE OF BEAUTY: A MIDSUMMER WALK ON HAMPSTEAD HEATH

*All things bright and beautiful,
All creatures great and small,
All things wise and wonderful:
The Lord God made them all.*

Hymns for Little Children; Cecil Alexander 1848

One of my earliest memories was singing this hymn at morning assembly in my infants' school in a small town near Birmingham in about 1944/45. My father sent us there to escape the blitz in London. The hymn had a very catchy melody that I can remember to this day. My wife has the same memory from her infancy in Newcastle upon Tyne. It was written by Cecil Alexander in 1848 about 10 years before the publication of Charles Darwin's "On the Origin of the Species", at the very time that Darwin was struggling to come to terms between the received wisdom about the creation and his new theory of evolution. His struggle was not helped by the anti-science lobby lead by the romantic poets of the day.

*Do not all charms fly
At the mere touch of cold philosophy?
There was an awful rainbow once in heaven:
We know her woof, her texture; she is given
In the dull catalogue of common things.
Philosophy will clip an Angel's wings,
Conquer all mysteries by rule and line,
Empty the haunted air, and gnomèd mine—
Un-weave a rainbow, as it erewhile made
The tender-person'd Lamia melt into a shade.*

"Lamia" by John Keats 1820

The verse above is an extract from Keats' epic poem "Lamia", the serpent turned woman. The poem is based on a Greek myth and is meant to be allegorical. I take it as a reference to the serpent in the Garden of Eden encouraging Eve to seduce Adam into taking a bite from the fruit of the "Tree of Knowledge", as described in the first chapter of Genesis. It is also a sideswipe at Sir Isaac Newton for "un-weaving the rainbow" and perhaps an allusion to the eureka moment when Newton observed an apple dropping from a tree in his orchard. One assumes that Keats would have approved of the sentiments of Cecil Alexander's childish appreciation of "God's" creation and regret that mankind was cursed with the fruits of the tree of knowledge had he lived long enough. Sadly, Keats died in 1821 at the age of 26 from pulmonary tuberculosis his mother having died of this scourge when he was 14. It is worth noting in passing that Keats trained as a doctor at Guys Hospital, but nothing on offer in that benighted era of medicine, could have had an impact on the inevitable progression of his terminal disease. About 125 years after the death of our beloved English romantic poet, scientists at the Medical Research Council, conducted the first randomised controlled trial that involved streptomycin for the treatment of pulmonary tuberculosis, since when tuberculosis can be considered a curable disease. "Consumption" no longer consumes romantic poets like Keats, graphic artists like Aubrey Beardsley (1872-1898), Botticelli model Simonetta Vespucci, not to mention fictional heroines of grand opera, like Mimi and Violetta, all of whom died before the age of 30. I think we would agree that the world is a better place for this small mercy.

You might at this point be wondering what any of this must do with the understanding of breast cancer. I'm trying to make two points. Firstly, that some knowledge of the evolutionary process will help the reader understand how the beautifully organised systems of the human body came about. Secondly, I've provided an example of a clinical trial that saw the beginning of the end of a very common lethal disease.

Evolutionary Advantage: Fibonacci sequence, the Golden Ratio, Fractal Geometry and our Concept of Beauty

The passage below is from Darwin's "On the origin of species" (1859). He beautifully, and with a remarkable economy of words, describes the hypothesis that launched a scientific revolution.

As many more individuals of each species are born than can possibly survive; and as, consequently, there is a frequently recurring struggle for existence, it follows that any being, if it vary however slightly in any manner profitable to itself, under the complex and sometimes varying conditions of life, will have a better chance of surviving, and thus be naturally selected. From the strong principle of inheritance, any selected variety will tend to propagate its new and modified form.

Charles Darwin 1859

Let me start by providing a good example of how the evolutionary advantages of random errors in the copying of DNA have led to the appearance of organisms of increasing complexity and how this is linked to our concept and appreciation of beauty. In chapter two you will then get a better understanding of the external and internal anatomy of the human breast. But first let me teach you something about fractal geometry.

Fibonacci was a mathematician who lived in Pisa in the late 12thC who achieved immortality as his name lives on in the “Fibonacci sequence”. This mathematical construct has origins in ancient Hindu-Arabic numerical system. The sequence is made up of numbers that are derived by the summation of the two numbers preceding it in the sequence.

It starts off like this: $1+1=2$; $1+2=3$; $3+2=5$; $5+3=8$... After say 20 iterations you arrive at the large number 6765. (See panel below)

F_0	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}	F_{11}	F_{12}	F_{13}	F_{14}	F_{15}	F_{16}	F_{17}	F_{18}	F_{19}	F_{20}
0	1	1	2	3	5	8	13	21	34	55	89	144	233	377	610	987	1597	2584	4181	6765

Mathematicians who have too much time on their hands, like to play around with this sequence for all sorts of esoteric fun and games. My interest however lies not so much in the sequence itself as to the ratio of the larger of any couplet over its smaller preceding number. For example, $6765/4181 =$ approximately 1.618. But wait a moment, let's try $377/233$. That also approximates to 1.618. Apart from the first few numbers that provide you with a ratio close to 1.6, all other ratios end up with an "irrational number" (never ending) taken to the 8th decimal point on my smart phone calculator of 1.61803396. This number is referred to by the Greek letter phi (ϕ).

Most paperback books measure 8 x 5 inches whilst credit cards often measure 8x5 cm. From the time of the ancient Greeks this ratio has been recognised as the key to our understanding of beauty. The Ancient Greeks called it the "divine ratio" whilst the artists and architects of the renaissance called it the golden ratio or sometimes the golden section. Next time you wander round an art gallery in your mind's eye measure the frames of the pictures on the wall. In my study as I glance around, I can count 10 pictures if I include photographs, six of which carry a ratio of about 1.6. I live in a Georgian house that obeys the architectural strictures of Palladio. As I look through my window towards Hampstead Heath, I note that the window aperture has the right proportions and that it is broken up into 24 small window panes that follow the same pattern.

When it comes to understanding the composition of fine art you might as well make a start with Mondrian whose work is full of rectangles that reflect the golden ratio. Sometimes the work is subtler in its adherence to the teachings of Palladio and my guess is that the artist was not deliberately dividing up his canvas with a compass or set square, but by trial and error, and with preparative sketches, arrived at a composition that was pleasing to the eye. As an example, take Vermeer's painting of a young woman reading a love letter facing the light coming from an open window on the left side of the canvas.

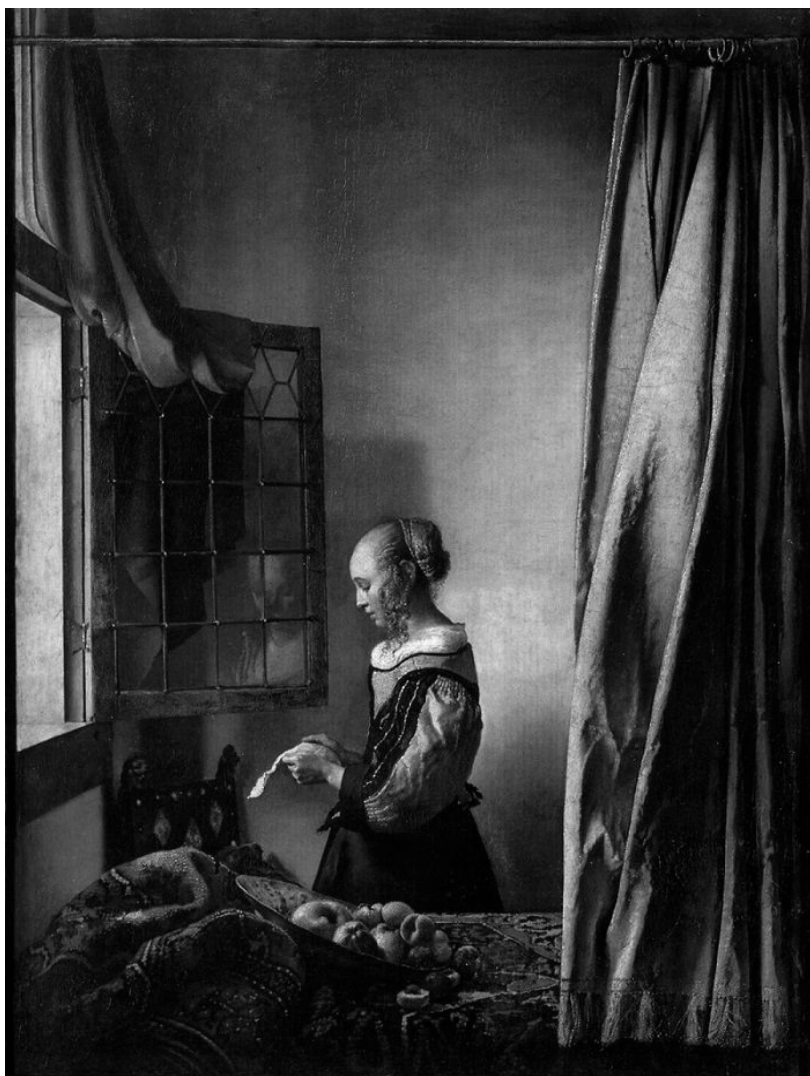


Figure 1

It's in the Dresden State Art Museum. I once made a careful copy of this work as an apprentice artist. Because I was studying the work closely as a copier, I could make out the rectangle that fixed and rested the image of the central figure. The window and the window panes are seen obliquely so in fairness you can't confirm that they are the right proportions to support my conjecture, but if you look at the rectangle made by the vertical drop of the heavy silk curtain and the horizontal made by the thick woven covering of the table bearing a plate of fruit you will see a perfect ratio of just a little over 1.6. I confirmed this, not by the naked eye estimate, but by using my callipers.

Spirals and Fractal Geometry

There are two other phenomena linked to the golden ratio I would now like to describe; spirals and fractals. If you take a rectangle that conforms to the golden rule and then divide it in two along the long side, you end up with two rectangles that share the ratio. If you take the smaller of the two rectangles and section it again at the same ratio, you end up with two smaller rectangles. You can continue the process again and again and still the pattern is repeated until the process comes to an end limited by your eyesight, the accuracy of your callipers and the thickness of your pencil point. With a magnifying glass and the technical skills and equipment of a watchmaker, you might repeat the process for a couple more iterations. If you now draw quarter circle arcs connecting the opposite corners of each family of rectangles, they link together as a perfect spiral.

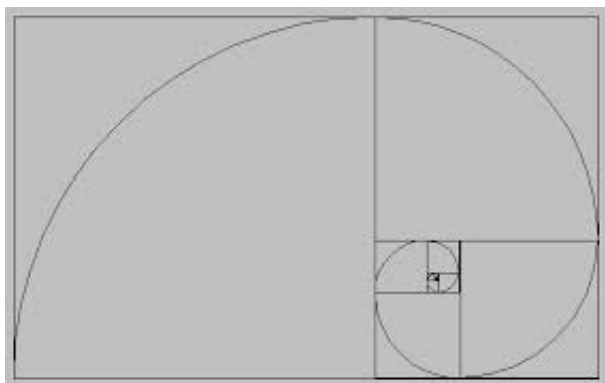


Figure 2

That is described as the golden spiral. The ratio of the lengths of the arcs with each turn of the spiral is again approximately 1.618. The common properties of the sectioned rectangle and the golden spiral is self-similarity at each magnification.

To provide these arcs with the ratio 1.618 you can cut a circle of any size with a pair of radiuses extending from its centre at an acute angle of 137.5° and its complimentary obtuse angle of 222.5° , the ratio of the acute angle over the obtuse angle is $1/\phi$. 137.5° is known as the golden angle. If you then take a vertical line of any length and bifurcate it at the golden angle and add branches of a length ratio to the original stem of $1/\phi$ (0.618) and reiterate the process to a level of your visual acuity, you will have created a tree like form that is self-similar at every degree of magnification.

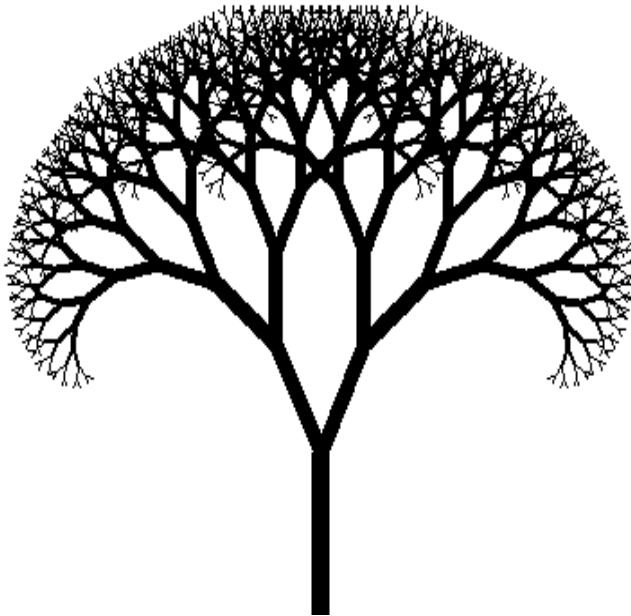


Figure 3

This property is known as fractal geometry and is ubiquitous in nature and our concepts and appreciation of beauty. Armed with these instruments of observation, a simple appreciation of the principles of Darwinian evolution, an open mind as well as eyes wide open, I will take you on a guided walk through my favourite places on Hampstead Heath.

In the long bright summer evenings after and long hard day in the operating theatre or seeing outpatients in central London, I would often get off the Northern line tube at Hampstead, one stop before Golders Green the station nearest my home, in Hampstead Garden Suburb.

From there I would enjoy a delightful walk taking about 30 minutes, through a section of Hampstead that is rarely visited by strangers. To start with I'd walk up the steep hill of Heath street passing the art galleries, coffee shops and an unwelcome plethora of estate agents. At the very top of the hill lies Whitestone pond with its flag-mast marking the highest point in north London. From this vantage point there are spectacular views of the City of London and Canary wharf looking to the south. Nearby is the charming old pub with New England style timber cladding, named after Jack Straw who led the peasant's revolt in the 1381. You then turn half right and start walking along the north side of Spaniards Road in the direction of the old toll gate. After about 30 paces there is a gap in the wooden barrier that leads down a steep path to Sandy Heath. From there I walk along a network of half overgrown lanes, is a nature trail that I usually have to myself. Although retired from clinical practice, I keep up this habit at any excuse on my return from a visit to town. These days I can do this at leisure and in the manner of a Victorian natural history scholar, I interrupt my reverie to make notes of my scientific observations along the way. Half way on my journey the steep slope of the north facing escarpment flattens out into a sylvan glade surrounded by giant 150 to 200-year-old oak trees.

In the centre of the glade is a pond. This is not a natural pond but a flooded gravel pit. In the middle of the 19thC when the Victorian Gothic masterpiece of St Pancras station was being built, the gravel to make the cement was dug out from this space, turning an area of meadowland into a valley. Underground rivulets, draining down from the watershed along Spaniards Road, filled up this valley and fed the saplings that ultimately grew into the great oaks. This serene and pretty sanctuary reminds me of the scenery of the first act of Swan Lake or the setting for "A midsummer's night dream". The pond has no name so I call it "No Name" pond. The pond changes magically during the four seasons. In the winter, it freezes over and red notices come into bloom warning that the ice is thin. There have been tragic drownings in the past. In spring the ice melts and in the phase before the oaks are in full leaf, the pond makes a perfect mirror only flawed by the ripples of the rising fish and the foolish flying insects. In midsummer, the pond suddenly transforms itself into an ersatz meadow as if in memory of the time before St Pancras was built. The