

PULMONARY NODULES AND THE FLEISCHNER RECOMMENDATIONS



“Head of a (Fallen) Angel”, pencil and charcoal on paper, 1887, Mikhail Aleksandrovich Vrubel.

*Of man’s first disobedience, and the fruit
Of that forbidden tree; whose mortal taste
Brought death into the world, and all our woe,*

*With loss of Eden, till one greater man
Restore us, and regain the blissful seat,
Sing Heav'nly Muse, that on the secret top
Of Oreb, or Sinai didst inspire
That shepherd, who first taught the chosen seed,
In the beginning how the heav'ns and earth
Rose out of chaos: or if Sion hill
Delight thee more, and Siloa's brook that flowed
Fast by the oracle of God: I thence
Invoke thy aid to my advent'rous song,
That with no middle flight intends to soar
Above th'Aonian mount, while it pursues
Things unattempted yet in prose or rhyme.
And chiefly thou O Spirit, that doest prefer
Before all temples th'upright heart and pure,
Instruct me, for thou know'st; thou from the first
Wast present, with mighty wings outspread
Dove-like sat'st brooding on the vast abyss
And mad'st it pregnant: what in me is dark
Illumine, what is low raise and support:
That to the height of this great argument
I may assert Eternal Providence,
And justify the ways of God to men.*

Opening lines of "Paradise Lost", John Milton, 1667.

Thus begins John Milton's monumental "Paradise Lost", of 1667, a work that Professor of Philosophy, Anthony O'Hear, ranked among the 19 greatest works of Western literature. Milton set out to emulate the grandest classical epics of Homer and Virgil, but wanted to tackle a subject that was not bound to any nation, but rather held a universal and timeless theme. In this sense he hoped that his work would surpass even the ancients. He laboured for the best part of the last twenty years of his life. His theme would be something none previous had even dared contemplate, let alone attempt, not even the immortal Dante Alighieri - a justification of the ways of God to men. And he would narrate a tale, not recorded in any detail in the sacred scriptures - a monumental epic of a time before the beginning of the world - a time before Genesis. He would tell of a great battle before time, that of the Rebel Angels against God and by so doing he would bring us to an understanding of the "ways of God". The result would be something intensely unsettling, and remains disturbing even to modern readers who understand the contradictions within it! Scholars have debated its "true" meaning for centuries and this debate continues unresolved to the present day.

This battle would be no ethereal struggle of philosophy, but a real blood and guts battle between legions of supernatural beings, swords in hand, a fight to the death. The leader of the Rebels against God, was an Angel named Satan. He questioned blind obedience. He had a thirst for knowledge, but God would not allow this. Satan questioned why, but to no avail. "We are all equal beings, what sets you apart", he asked? Why is knowledge so dangerous? God threatened to cast him out of heaven, but soon other Angels began to

back Satan up, demanding equal status and equal knowledge of the Universe. The vast host of Angels split ranks into those who gave unquestioning loyalty to God - and those who questioned blind subservience. "Are we to be slaves?" they asked. Milton lived at the dawn of the scientific enlightenment. Questions about the nature of the Universe were being asked, and the answers that "natural philosophy" (i.e proto-science) were providing very often seemed to be at odds with the established teaching of religion. To some few in the Seventeenth century, and to most in the 21st century, Satan, rather unsettlingly, begins to emerge as a voice and a hero for the oppressed!

The battle is protracted and bloody. God's legions are led by the Archangels Michael, Gabriel and Raphael, those of Satan's by Belial, Moloch, Mammon, and Beelzebub. In the end God proves too strong and the Rebel Angels are cast out of Heaven into the horrific black abyss of Dante's Inferno for all eternity. To take the place of the fallen Angels, God creates humanity in the form of Adam and Eve. But instead of placing them in Heaven, he places them into the Garden of Eden, where they must prove their unquestioning loyalty and obeisance. And it is precisely here that the unsettling nature of Milton's work takes another step up. Satan, even though defeated, still will not yield. He will rule in Hell, and he will warn Adam and Eve of the servitude they face. He shall show them the "Tree of Knowledge"- why live in ignorance? Again to a modern mind Satan appears disturbingly as the "hero" - he tries to warn Eve, as if perhaps to "liberate" her from an eternity of ignorant servitude in a false "Matrix" type world in the parlance of the 21st century. Eve succumbs, and using her "charms", seduces Adam into also eating of the Tree of Knowledge. Herein lies the paradox.

Unquestioned obedience to divine omnipotence was taken for granted by most in the Seventeenth century, but in the emerging scientific age, old certainties were being questioned. Dante struggled with the same issue in the early Fourteenth century, at the dawn of the Renaissance, also a great age of new learning and questioning. But rather than ask the difficult questions - as Milton did - Dante simply resolves the issue by the "divine revelations" he receives during his terrifying journey through the afterlife. Rather astonishingly, to modern sensibilities, we find the classical hero Odysseus in Dante's Hell! His great sin? To ask questions! In the form of his great Odyssey, he seeks to understand the larger world, which he has no business in doing! Trust in God should be enough. He even ventures beyond the known world - beyond the Pillars of Heracles - but God says enough! He kills Odysseus and all of his crew and sends them to Hell! Odysseus of course to the modern mind is seen as a hero for his epic voyage of discovery; but then isn't this exactly what Satan was striving to do? More modern writers in fact, have unambiguously come out as depicting Satan as the true "hero" of Milton's Paradise Lost. William Blake, after reading it, concluded that Milton was actually "of the Devil's party", though "without knowing it". For Percy Bysshe Shelley, Milton's Satan was actually a moral being!, "one far superior to his God", and one who "perseveres in some purpose....in spite of adversity". A most admirable quality. He depicts God as uncaring of the horrible fate he has ordained for Satan. God is complacent, "in the cold security of undoubted triumph". We have only God's word that knowledge is bad. History, Shelley is saying, is written by the victors.

God of course redeems humanity through the suffering and death of his son in the mortal world. But still Satan will not yield. It is at this point that Milton makes his case. While at

first we may have had some faint and secret sympathy for Satan, now he is simply going too far. If Satan cannot regain Heaven - then neither will humanity. He will drag humanity down to Hell with him, out of sheer spite and cold revenge - and so the eternal struggle of good and evil ensues on Earth.

But has Milton really achieved his stated aim - "to justify the ways of God to men"? The so called eternal struggle of "good versus evil" could also be read in a more modern sense as the age old Platonic versus Aristotelian struggle - read faith versus science. Yes God is victorious in the end and Satan "loses the plot" - but does this justify Gods actions? Why does all humanity suffer for the "sin" of Adam and Eve?. Why does questioning God earn eternal damnation of unspeakable torment? This is the great central debate in Paradise Lost.

The whole monumental epic takes on a special poignancy indeed when we understand more of Milton himself. He wrote his Magnum Opus over twenty long years. The last of which he was blind and so had to dictate his words making his work all the more remarkable. But Milton himself had worked closely with the Cromwellian Republic in the decade before he commenced Paradise Lost. Many were surprised that he survived the transition of government back to the Monarchy under Charles II. He had approved of the execution of Charles I. Dante had struggled mightily with his sin of pride (and probably of lust). As Dante feared for his immortal soul, did Milton so fear for his almost four centuries later? Now he was soon to meet his maker - was he having Dantean nightmares of how God would judge him - locked in his sightless world amid terrifying visions of eternal damnation? Did he live a good and obedient life? Well no - he was a regicide after all! He too had rebelled against his rightful master, and a master at that, who had ruled by unquestioned "divine right". Isn't that the very thing Satan had done?

In the end did Milton really explain the "ways of God to men"? We are left in an uncertain and unsatisfied state. Valiant though his attempt was, perhaps it was doomed to failure from the outset. As O'Hear points out, "that may be because the endeavor itself, if honestly undertaken, is impossible".

When we read the radiological report "pulmonary nodules - please follow-up" we are left in an uncertain and unsatisfied state. We seek justification in the mysterious ways of the Radiologist! Fortunately we have at our disposal the Fleischner Recommendations - a somewhat more satisfying justification than Milton's "Paradise Lost".

PULMONARY NODULES AND THE FLEISCHNER RECOMMENDATIONS

Introduction

Pulmonary nodules (sometimes also referred to as “spots on the lung” or “coin lesions”) are small rounded opacities seen on CXR or CT imaging of the lung.

The term pulmonary nodule is just a **radiological label**, *not* a pathological diagnosis. There are many pathologies that can give the radiological appearance of a nodule.

As the spatial resolution of CT scanners continues to improve, radiologists are reporting more and more of these most often as an **incidental finding**.

From a **pathological** viewpoint the most important classification of these lesions will be that of **benign** versus **malignant**.

Incidental lung nodules are encountered *commonly* in routine cross sectional imaging.

The risk of developing cancer in very small nodules (< 5 mm) is very low.

Traditionally clear-cut recommendations about what to do about these nodules was lacking and in fact there was high variation in practice amongst reporting radiologists, as to what follow-up was required.

As a result, it became common practice for the radiologist to simply make a “note” of these nodules in the report and move on, leaving the ball in the clinician’s court to decide whether to follow them up and at what interval.

The **Fleischer Society Pulmonary Nodule Recommendations** were developed to assist clinicians in planning the most appropriate follow up of a radiological nodule.

Radiological Classification of Pulmonary Nodules

Pulmonary nodules can be **radiologically** classified a number of ways including:

1. Size:
 - Miliary nodules: < 2 mm
 - Pulmonary micro-nodule: 2-7 mm
 - Pulmonary nodule: 7-30 mm
 - Pulmonary mass: > 30 mm (i.e. > 3 cm)
2. Morphology:
 - **Solid pulmonary nodules**

- ♥ Including calcified pulmonary nodules
 - Partly solid pulmonary nodules
 - Ground glass pulmonary nodules
3. Distribution:
- Perilymphatic pulmonary nodules
 - ♥ Perifissural pulmonary nodules
 - Centrilobular pulmonary nodules
 - Random pulmonary nodules

Pathological Classification of Pulmonary Nodules

Nodules most commonly represent a benign lesion but in some cases could represent a malignant cancer.

Benign lesions can include:

1. Fibroma
2. Hamartoma:
 - A benign focal tissue malformation
3. Autoimmune diseases:
 - Wegener's granulomatosis
 - Sarcoidosis
 - Rheumatoid nodules
4. Infections:

Most infections that appear as pulmonary nodules are relatively indolent and often not active.

Inflammation related to these infections often forms a granuloma. Granulomas form when the immune system isolates substances that it considers foreign.

Most of the time granulomas occur in the lungs, but they may also form in other parts of the body.

They can become calcified over time, as calcium tends to collect in the healing tissue.

Examples include:

- Mycobacterium
 - ♥ Mycobacterium tuberculosis
 - ♥ Mycobacterium avium intracellulare
- Fungal infections:
 - ♥ Aspergillosis
 - ♥ Histoplasmosis
 - ♥ Coccidiomycosis
 - ♥ Cryptococcosis.

Malignant lesions can include:

1. Primary lung cancers
2. Lymphoma
3. Carcinoid (a small, slow-growing cancerous tumor)
4. Sarcoma (a tumor consisting of connective tissue)
5. Metastatic secondaries

Nodule Assessment

Over 90 % of pulmonary nodules that are smaller than 2 centimeters in diameter are benign.

The larger the nodule is, and the more irregularly shaped it is, the more likely it is to be malignant.

A pulmonary **mass** (i.e. radiographic lesion of > 3 cm) is more likely to represent a **cancer** than is a nodule.

Though most lung nodules are not malignant, it is very important the those representing cancer are identified early in their course, when they are potentially curable.

In general, malignant nodules double in size every 1 - 6 months. Nodules with a slower or faster growth rate are less likely to be cancerous. Comparison with old images is useful, when or if these are available.

If the nodule does **not grow** over time, it is generally confirmed to be benign.

In general terms the interval between repeat scans and the length of follow-up will depend on the size of the nodule and the risk profile a patient has for malignancy.

The Fleischner Society Pulmonary Nodule Recommendations

The **Fleischner society pulmonary nodule recommendations** are usually for follow-up and management of newly detected pulmonary nodules:

- Smaller than **8 mm** (detected incidentally on a non-screening CT scan).
- In patients ≥ 35 years

Excluded are:

- Patients with an unexplained fever
- Known or suspected cancer outside of the lungs

The recommendations are based on:

- Size of nodule
- Nature of the nodule
- The risk profile of the patient, (see below for these).

The recommendations are:

For Solid Nodules:

Nodule Size	Low Risk	High Risk
≤ 4 mm	No follow-up needed.	Follow-up CT at 12 months and if no change, no further imaging needed
4-6 mm	Low risk patients: follow-up at 12 months and if no change, no further imaging needed	High risk patients: initial follow-up CT at 6-12 months and then at 18-24 months if no change

6-8 mm	Low risk patients: initial follow-up CT at 6-12 months and then at 18-24 months if no change	High risk patients: initial follow-up CT at 3-6 months and then at 9-12 and 24 months if no change
> 8 mm	Follow-up CTs for low and high risk patients at around 3, 9, and 24 months Consider dynamic contrast enhanced CT, PET, and/or biopsy	

If a nodule up to 8 mm is not purely solid, but rather *partly solid* or is *ground glass* in appearance, further follow up is required *after 24 months* to exclude the possibility of a slow growing adenocarcinoma, (see below):

For Solitary pure ground-glass nodules:

- For nodule size ≤ 5 mm:
 - ♥ No CT follow up required
- For nodule size > 5 mm:
 - ♥ Follow up CT at 3 months, then annual CT for at least 3 years

For Solitary part-solid nodules:

- Initial follow-up CT at 3 months
- If persistent and solid component < 5 mm
 - ♥ Annual CT for at least 3 years
- If persistent and solid component ≥ 5 mm
 - ♥ Biopsy or surgical resection

For Multiple subsolid nodules:

- Pure ground glass nodules ≤ 5 mm
 - ♥ CT at 2 and 4 years
- Pure ground glass nodules > 5 mm, without a dominant lesion(s)
 - ♥ Initial follow-up CT at 3 months, than annual CT for at least 3 years
- Dominant nodule(s) with part-solid or solid component

- ♥ Initial follow-up CT at 3 months
- ♥ If persistent, biopsy or surgical resection (especially if has >5 mm solid component).

High Risk Factors:

High Risk Factors for malignancy include:

1. Smoking
2. Elderly
3. History of malignant disease
4. First degree relatives with lung cancer.
5. Environmental exposures:
 - Asbestosis
 - Pneumoconiosis
 - Radiation hazards

Follow-up Investigations

Options include:

Repeat CT Scans:

CT scans are more accurate than chest x-rays in determining the nature of the nodule.

A CT scan can find very small nodules, as small as 1-2 mm in diameter.

PET Scan:

A PET scan can also help to find out if a nodule is malignant or benign.

A PET scan uses a radiolabeled substance such as glucose that is absorbed by the nodule, and able to be imaged, providing a picture of the nodule's metabolic activity level.

Malignant cells tend to have faster metabolic rates than normal cells, so they require more energy and thus absorb more of the radiolabeled substance.

Nodules can light up on PET imaging if they are **malignant** or if there is **active inflammation**.

Nodules smaller than 8-10 mm however are not seen well by PET imaging.

Bronchoscopy:

This may be appropriate in some cases to obtain tissue samples

Needle Biopsy:

Needle biopsy, also known as transthoracic needle aspiration, this test is most successful when the nodule is towards the edge of the lung, near the chest wall.

A needle is inserted through the chest wall and into the nodule, under the guidance of a CT scan, and a tissue sample is taken for histological examination.

Surgery:

If the nodule has a concerning appearance and/or growth pattern, or it is somewhat concerning and its nature is not able to be clarified by the above tests, then the best step may be to remove the nodule. This will clarify its nature while treating it. This requires the patient to be fit enough to undergo the surgery.



“Satan presiding at the Infernal Council”, mezzotint, 1824, John Martin, Victoria and Albert Museum

....Farewel happy Fields

*Where Joy for ever dwells: Hail horrors, hail
Infernal world, and thou profoundest Hell
Receive thy new Possessor: One who brings
A mind not to be chang'd by Place or Time.*

*The mind is its own place, and in it self
Can make a Heav'n of Hell, a Hell of Heav'n.*

*What matter where, if I be still the same,
And what I should be, all but less then hee
Whom Thunder hath made greater? Here at least
We shall be free; th' Almighty hath not built
Here for his envy, will not drive us hence:
Here we may reign secure, and in my choyce
To reign is worth ambition though in Hell:
Better to reign in Hell, than serve in Heav'n*

“Paradise Lost”, Bk IV -249 - 263, John Milton, 1667.

References

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