[Note – I may have driven roughshod over copyright claims and hope you will remember this. The origin links are added.]

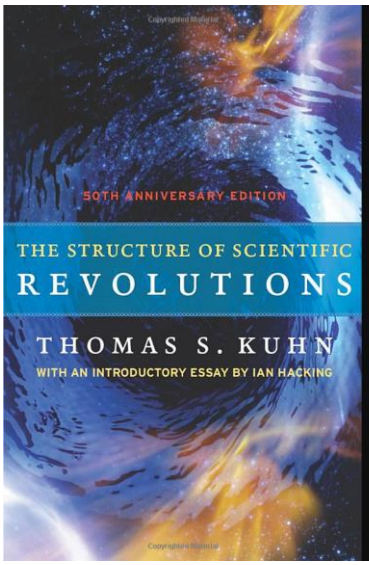
What gets the immune system up in arms?

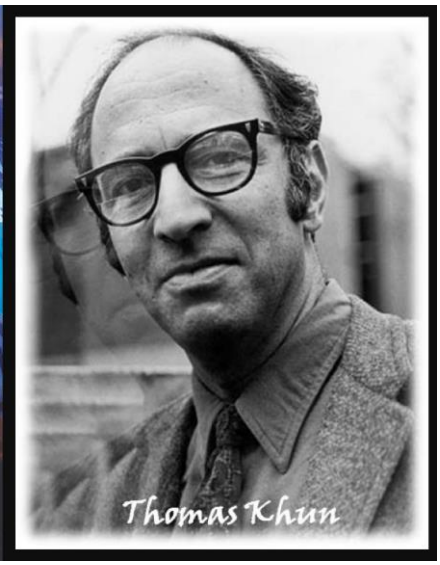
And what turns the heat down?

First I'm assuming my opinion is right. This assumption removes padding but it also obliges you to believe nothing until you trust it.

So what's the message?

Immunology is on the cusp (or process) of a major scientific revolution; Thomas Kuhn popularised such revolutions as paradigm shifts. It does not matter who may have presented or propagated it; it matters that you focus your attention on it.

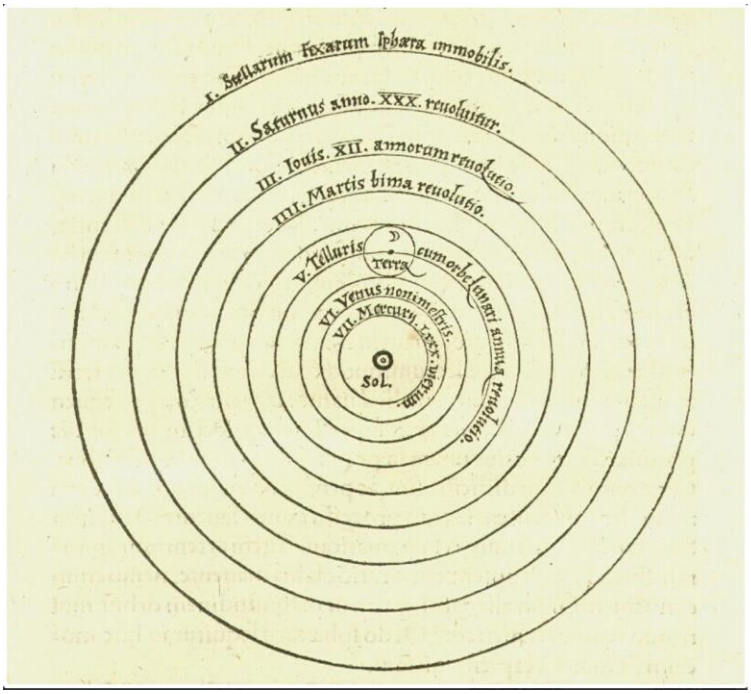


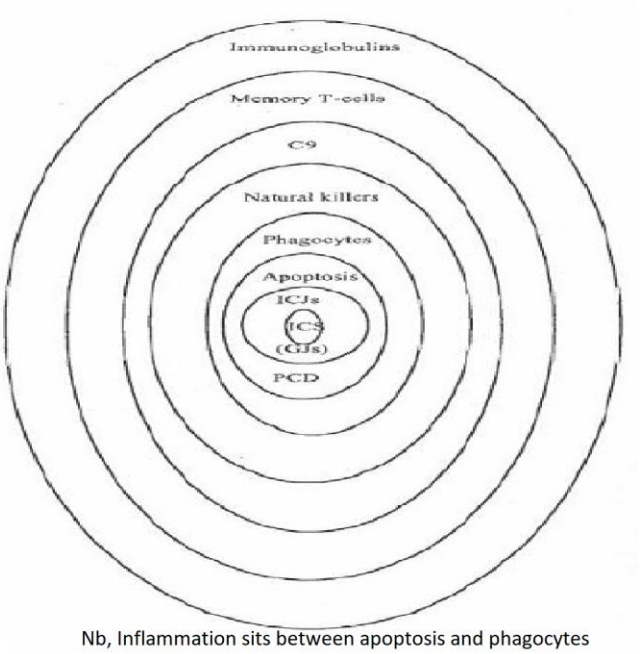


Just as Copernicus challenged the perspective of an Earth centred firmament, immunology is headed for its own revolution. For historical reasons – the whole of the immune universe came to be focused around lymphocytes, antibodies and adaptive immunity. Up until the last few years it has been considered to be a lymphocyte centred (lympho-centric) universe that revolves around a "bug" hunting, chasing and killing system ("and, by the way – in addition, it also discriminates self molecules for non-self molecules"). My belief is that the discipline has driven itself up a blind alley from which it is hard to abandon this view.

I propose that this old perception is plain wrong. The system, instead, is hell bent on integrity and homeostasis. At its core sits inflammation – it's an inflammo-centric system (in analogy to a helio-centric solar system). Phagocytes are its chief executors. All else is satellite stuff that stacks up to enhance the function and efficiency of inflammation. I have recruited the term "morphostasis" to describe it.

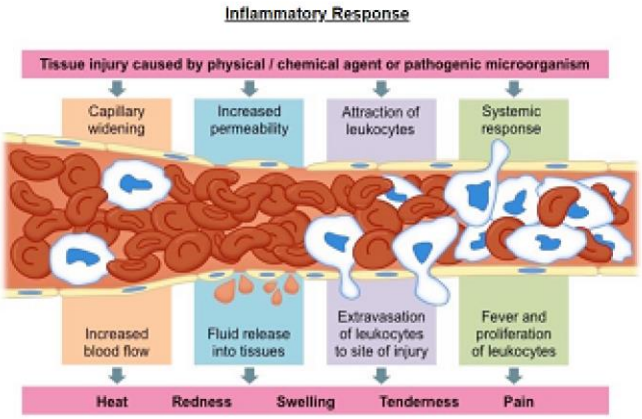
Thomas Kuhn talked of "tautologies" as situations that, in retrospect, should never have been seen otherwise. This highlights the problem science has with hidden assumptions. Until you understand how an assumption has blinded you, you cannot shed the blinders.





Nb, Inflammation sits between apoptosis and phagocytes

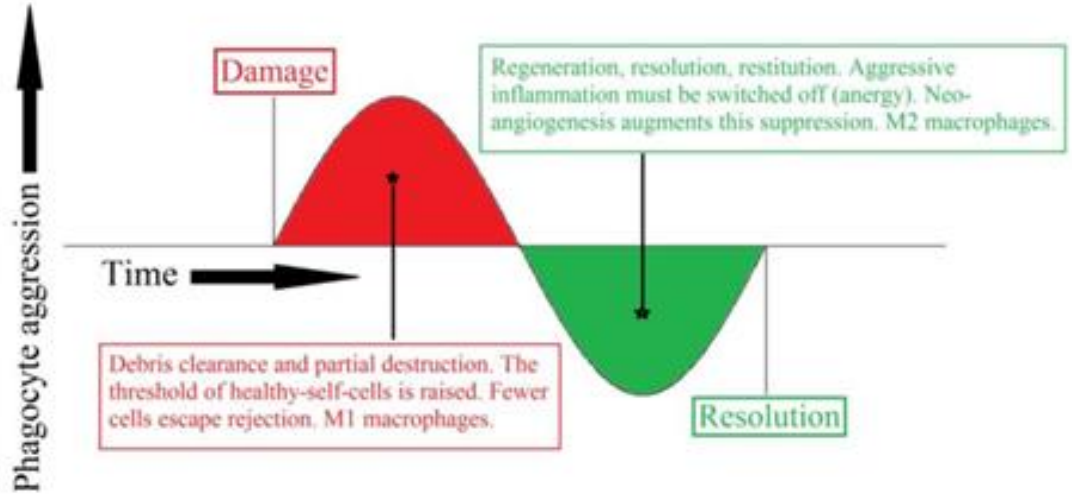
So – for those who aren't sure what inflammation is here's a resume.



[This is deliberately obscure. Go to:

https://ib.bioninja.com.au/standard-level/topic-6-human-physiology/63-defence-against-infectio/inflammation.html

for the original.]



Idealised representation of the inflammatory sequence

[Here's a reference that contains a more detailed representation of this sequence:

https://www.nature.com/articles/s41536-017-0023-2 - Figure 1]

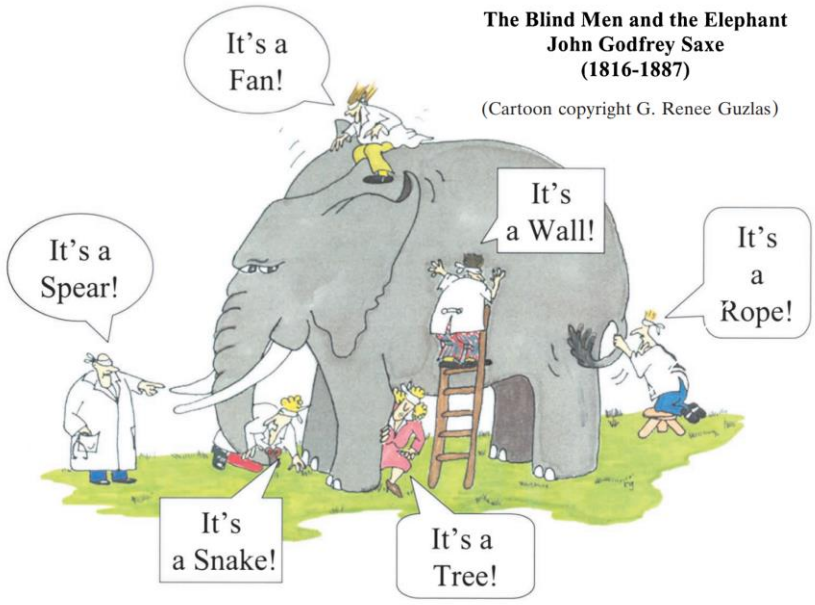
Whenever there is a disruption in the body, a stereotypical sequence begins. This starts with chemical and nervous alerting signals that broadcast "we have a problem". On this cue, the local small venules undergo changes. They swell to increase blood flow, they become leaky. Polymorhonuclear phagocytes latch on to the vessel wall then insinuate themselves between the lining endothelial cells to escape into and then invade the surrounding tissues. These phagocytes act like a pack of hungry wolves; they retain some sense of what a healthy-tissue-cell feels like and so avoid too much damage to them. Everything else, cells, organisms and biological debris is considered to be a feast to be devoured. Once this wave of polymorphs has done its job the polymorphs begin to commit suicide (mulching their contents) and the next ingress of phagocytes – the macrophages - sweep in. These clear away the dying polymorphs and continue the debridement of tissue debris. Self cells are not necessarily exempt from aggressive attention – particularly if they are sub-par. As the debridement subdues, so the macrophages change their behaviour from aggressive/destructive to nurturing/pro-regenerative. And the rebuild begins. Pain nerves become supersensitive so that any movement causes a discomfort that inhibits disruption of the resolution. The macrophages now take on a commanding role in reconstruction. Now a tolerant rather than aggressive milieu becomes important; this allows activated stem cells to go about the rebuilding without interference or suspicion.

As you are aware, from experience, this happens over 10 to 14 days. It becomes increasingly prolonged and less efficient as we age.

So, this is the core response and everything else is a satellite process. Adaptive immunity gives inflammation a memory so that it can turn on fast to caricature its response on any subsequent encounter with a similar sets of circumstances.

So how did we get to the point where we ignored the centrality and importance of this core process?

Science tends to grow by popular modes of investigation and – in particular – measurable parameters. The outcome can be that, at any particular point in the process, two things happen. First, there is an attraction towards dissective investigation. Focal things become known about in increasing detail and investigators may become engrossed in this local scenario. That is well emphasised in Godfrey Saxe's poem about the elephant and the blind men of Indostan.



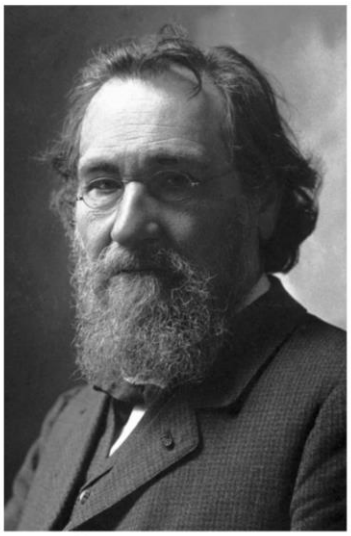
[Reproduced from: http://dx.doi.org/10.1046/j.1523-1755.2002.00600.x]

Each blind man is convinced their own perceptions are right and they are keen to dismiss other views. But ***we*** retrospectively have an overview of the elephant. Second, these focused investigations distort the overall process. An analogy is the representation of the body on the cerebral cortex. A fully functional and well-proportioned human (inset) is not apparent from this cortical representation.

[Reproduced from: https://en.wikipedia.org/wiki/Cortical_homunculus]

The adaptive immune system currently enjoys an exaggeration well beyond a tongue or a finger tip.

How did this distortion arise historically? Elie Metchnikoff is still the neglected hero of immunology who receives, mostly, lip service. He wrote extensively about the involvement of phagocytes in response to damage and to infective invasion. In a series of lectures, “The comparative physiology of inflammation” he made startling observations. These were side-lined for over half a century and are only just re-emerging in importance. They were ignored by a faction who believed that the serum factors were core and central in immunology. They believed that these were all that was needed to explain immunology. For them, Metchnikoff was misrepresenting and distorting things.



Ilya Ilyich Mechnikov
The Nobel Prize in Physiology or Medicine 1908

Born: 15 May 1845, Kharkov (now Kharkiv), Russian Empire (now Ukraine)

Died: 15 July 1916, Paris, France

Affiliation at the time of the award: Institut Pasteur, Paris, France

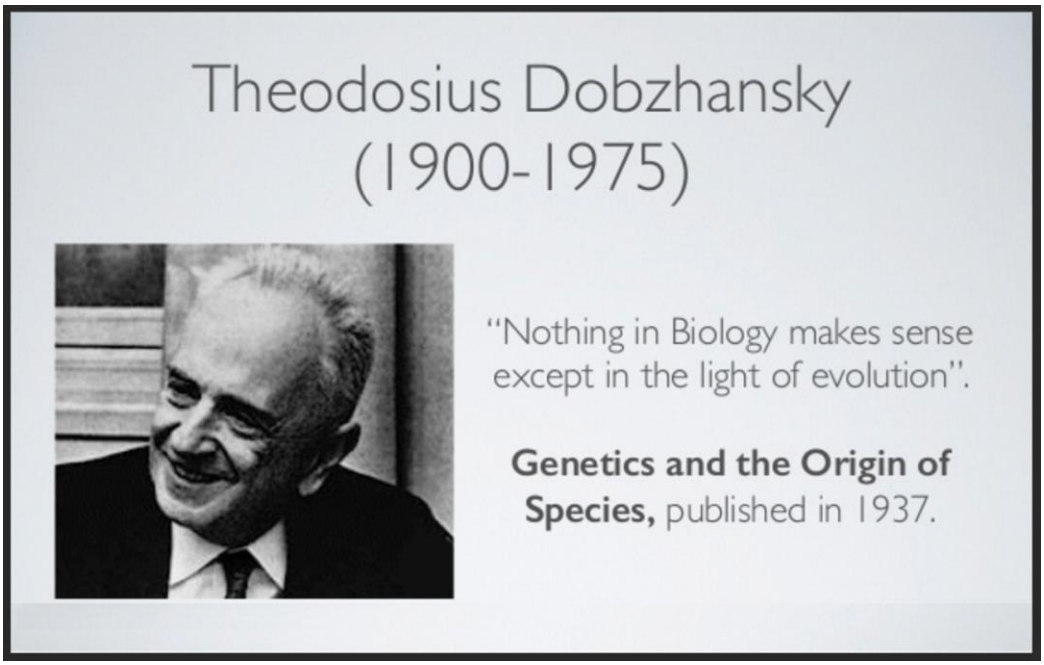
Prize motivation: "in recognition of their work on immunity."

Metchnikoff’s realisations included a bevy of observations.

- Inflammation responds to anything disruptive. That is:
- Damage
- Toxins
- Infections

- And etc
- He fully encompassed the importance of evolution and a comparative approach and in this respect foreshadowed this famous quotation that Tom showed earlier – but without my red emphasis.

"***Nothing*** in biology makes sense except in the light of evolution."
– Theodosius Dobzhansky, 1977



These phagocytic cells accumulate as the first responders to the site of disruption and set in motion

- Debridement
- Reconstruction
- And then restitution

For him, phagocytes and inflammation were the universe centre of immune activity. He realised it had functions

- in development (eg, tadpole tail resorption - and many others)
- in the maintenance of tissue integrity,
- in damage management
- in infection control.
- He even realised it may be important to debride damaged tissues to remove a potential growth medium for invading organisms (but had some doubt about its relevance).

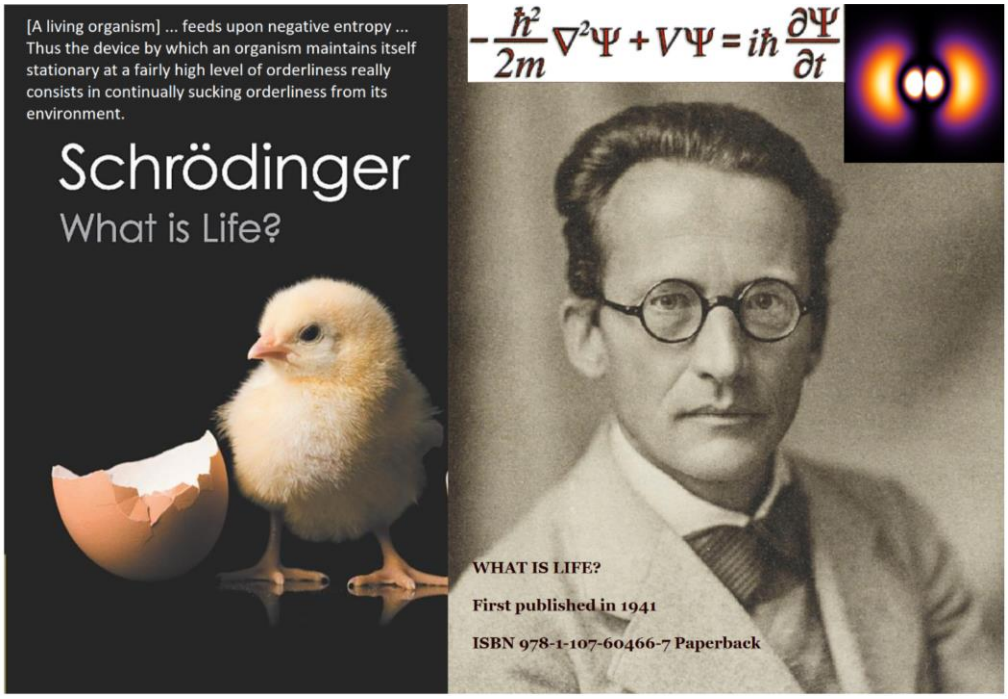
In 1908 the Nobel prize in Physiology and Medicine was jointly awarded to Metchnikoff and Ehrlich. We can split the then extant factions into the cellulists (the phagocyte protagonists) and the humoralists (the complement/antibody protagonists). I think Ehrlich was less condemnatory of the cellular theorists than many of his fellow humoralist protagonists. Whatever, "never the two shall meet" prevailed. I think the humoralists won out the next 40 and more years because it was more laboratory based and measurable. Metchnikoff's works was interpretative. So, his ideas went into eclipse and remained there until the second world war when Medawar, investigating burns and the potential of skin grafts, noticed the strong participation of cells in the rejection process.

In looking for an explanation that fitted well with the humoralists' views, immunologists began to think about self nonself discrimination. They swallowed the idea that molecules that T-cells recognise are sorted - one by one - into self or non-self. They had just learnt about the one lymphocyte one antibody idea. Also, studies on dizygotic calf twins showed that the foetal thymus was an important organ that oversees the reactivity of lymphocytes. It averts aggressive responses to self-tissues. The assumption was that self-reactive lymphocytes are culled. So, self nonself discrimination, by the mammalian foetal thymus, became

a de facto belief. This cull seemed to be supported by the intense lymphocyte death that was observed in the thymus (the lymphocytes that do apoptose are dominantly those that have no specificity for self-Mhc molecules).

The fulcral role of lymphocytes in the immune process became an accepted given. These cells were considered to be the ones that deliver aggression to pathogenic organisms and they were also responsible for graft rejection – a clear signal that they appeared to discriminate self from non-self epitopes. This cataloguing idea is beginning to appear quaint.

Between the 1970s and just into the 1990s inflammation was regarded as a parallel subplot - an also ran event - that was not intimately integrated with the adaptive immune system. The evolution of the adaptive immune system was regarded as a transitional new toy developed by evolution to give it massive advantages in dealing with "pathogens" and this was well beyond the capability of invertebrates. However, we now know that the lymphocytes that specifically respond to microbial threats use alpha-beta receptors that recognise oligopeptides in the groove of major histocompatibility (Mhc) molecules. These are only a subset of the retinue of lymphocyte lineages. Gamma delta T-cells are common. They do not recognise Mhc-peptides complexes. Instead they seem to be involved in innate protection of tissue homeostasis. And then there are a host of other innate lymphocytes and natural killer cells. Hmmm – something's suspicious with the old simplistic view here.



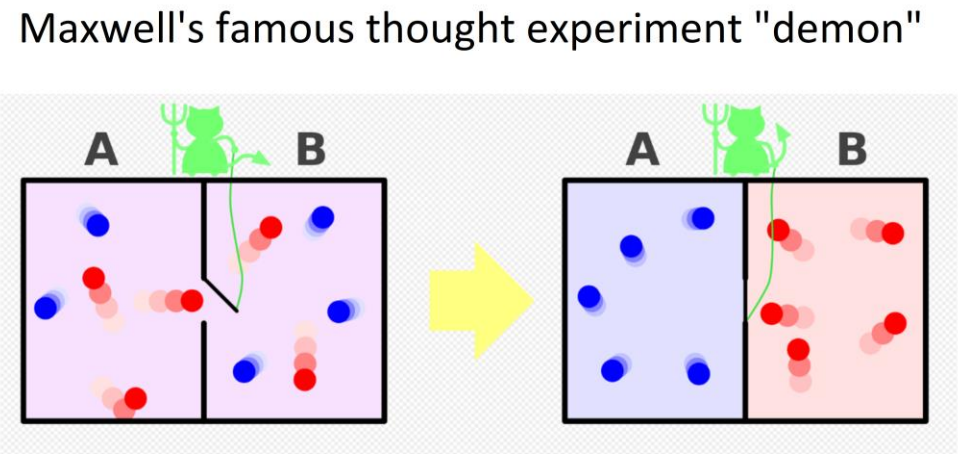
So let's go back to Metchnikoff's ideas on debris management and tissue debridement. This raises a window on entropy. Erwin Shrodinger famously stated,

"A living organism…feeds upon negative entropy… Thus, the device by which an organism maintains itself stationary at a fairly high level of orderliness (fairly low level of entropy) really consists in continually sucking orderliness from its environment."

Living organisms harvest energy and degrade it to less useable forms so they can claw their way up the maintenance-of-order gradient.

So what is entropy? It's a pity that it started out as an apparently positive concept whereas, in fact, it's a sort of negative. That makes it harder to juggle in our minds. The inversion, neg-entropy, was coined to better help us to think about the availability and utility of energy gradients. Low entropy energy sources are highly focal and concentrated (examples are a radiating Sun, a battery, a cylinder of super-heated steam) and it is then relatively easy to utilise an organised flow of energy as an "engine" for various processes. As we disperse strong and focalised energy (low entropy) along a gradient it becomes dispersed into progressively diffuse "microstates". So it becomes progressively harder to tap any contained energy as we shift along a useable gradient. It's really a probability thing. Isolated pockets of concentrated energy are

improbable states that prefer to flow to distributed, smaller and diffuse packets of energy. This flow is an asymptote towards the inevitable. Now, Brownian movement is a nice manifestation of microstates. Occasional individual molecule can have speeds way above the average. If we could somehow farm these highly energetic molecules, we could concentrate them up to do useful work.



But, it appears that sorting needs to disperse more energy than it is able to concentrate – otherwise we'd be on the way to a perpetual motion machine.

The idea, that entropy is synonymous with disorder, has been and remains popular. But, whilst entropy is, undoubtedly, the nemesis of order, this is only because order needs maintenance (and thus energy expenditure) or it will degrade and disperse.

Where do living organisms dominantly get their energy to construct biomolecules?

Living on mother Earth, our chief source of focal (low entropy) energy is radiated at us from the sun. Ultimately, nearly all life on Earth is dependent on some photosynthesising organism turning this radiation into utilisable biomolecules that are then bagged up in living cells. Those that are not primary photosynthetic producers need to find alternative "fuel" to survive.

Aside from the primary photosynthesising providers, the next largest block of living organisms rely on detritus (detritophiles). These live and persist by managing the decay of sun driven life that is, itself, a sort of half way house of "detritus" of degradation. The end of the journey is the final radiation of infra-red photons out into deep (intergalactic) space. Photosynthesisers provide detritophiles with degradable molecules that can be "burnt". The vast majority of detritophiles are patient. They wait for their meals to be offered rather than trying to invade a healthy organism before breaking it up. The ones that don't wait we grace with the terms pathogen (damage inducer), or herbivore or carnivore.

Dying animal cells release a bevy of "come and eat me" signals and surface molecules. The latter can fall into the Damage Associated Membrane Patterns molecules (DAMPs); Toll like receptors are often involved in identifying them. Bacteria display Membrane Associated Membrane patterns (MAMPs) that also interact with Toll like receptors. I like to think that this is a deliberate mimic (Trojan horse style) to have yourself invited in during the transition from life to death. Thus, you have a head start in the competition for resources; it doesn't matter that you lose family members who have tried to get in too soon – they are expendable so long as the advantage is gained.

The sanctity of life is a peculiarity of complex social animals and it reaches a zenith in socially advanced human societies. You cannot afford to wantonly throw away a lifetime of social skills and knowledge in

complex societies. However, sacrifice is freely embraced by many simpler organisms (including our own constituent cells) and used liberally to gain advantage for their species genome.

By extending Metchnikoffs's ideas, we can see that the inflammatory system and now, by implication, all the subservient systems are hell bent on beating back the tide of entropy. I have adopted the term morphostasis (trying to keep form constant). All organisms are successful at this as exemplified by their rapid disintegration after death.

So, if our response to invading micro-organisms is really an attempt to manage disruption, then we may not have a targeted attack on the pathogenic organisms themselves but on the pathogenic signature of the debris that they generate. This is a fundamental change from a deliberate bug targeted, chasing and killing immune response. They evoke responses because they are associated with detritus – not because they are micro-organisms. If a phagocyte comes across them it will chase them and devour them because it remembers its primordial origins as a unicellular amoeboid animal. But it doesn't need to enrol the adaptive immune system for that.

So what is the dominant meal for all our phagocytes?

- Is it bacteria?
- is it traumatically dying tissue?
- No!
- Every day it is estimated that one in 500 to one in a thousand of our own cells undergoes a controlled shutdown. This provides their dominant diet by far.

I have a black and white classification here in that we can divide death into a controlled shutdown ***apoptosis*** and a catastrophic ***necrotic*** demise. Modern research has uncovered many spectral variants on this; but this simplified classification will suffice for the present argument. The extraordinary things about apoptosis are

- that it is massive and can reach bizarre levels – particularly in the thymus.
- It is what has been termed "silent".
- Phagocytes and even adjacent cells clear this debris with barely a murmur of complaint from body systems.
- It is said that "it is immunologically silent" - but I reject this view.

All cell death leads to phagocyte processing and ultimately presentation to lymphocytes for memorising.

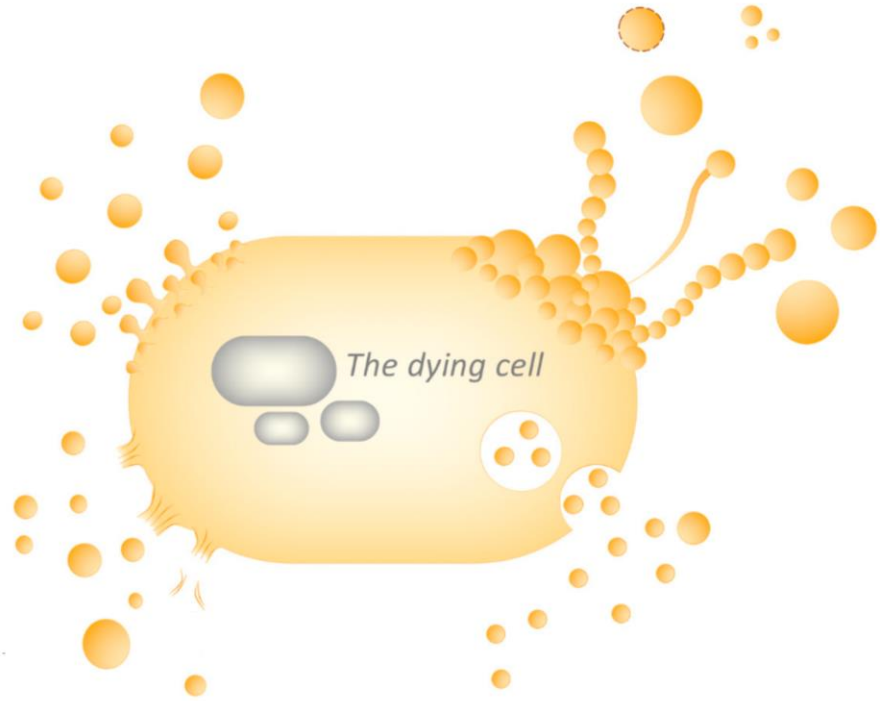
The general milieu predominating when phagocytic antigen presenting cells process the debris is logged. On meeting a precursor T-cell with an appropriate receptor (randomly generated) this cell is primed to reproduce that milieu on reencounter. So silent apoptosis leads on to the suppression of inflammation and messy spilt cytoplasm that is intensely inflammatory induces an aggressive and inflammatory response on reencounter.

So, die tidily and with minimal inflammation and the next time you are encountered you will suppress local inflammation. Should you die messily, shedding your contents then, the next occasion you are met, you will induce an aggressive pro-inflammatory response.

Now this sits nicely with what happens in the foetal thymus and, also, with what we call peripheral tolerance. On this view, logic would suggest that the extraordinary levels of apoptosis occurring in the thymus promote tolerance to any lymphocytes that meet their respective epitopes there. The old theories say that these lymphocytes die and are excluded from the repertoire. We have only to observe that the thymus generates copious suppressor T-cells to overthrow that perspective. And, it transpires, this is what happens. It is becoming increasingly clear that the thymus is a powerhouse of tolerant T-cell production.

Note what happens in systemic lupus erythematosus. There is often an abnormality of complement in this disease. Complement is important for rendering debris tasty to phagocytes. It aids the silent clearance of apoptotic cells and their exosomes. Leave this debris around too long and the membrane packets that are dispersing will start to burst and become hyper-immunogenic leading to an aggressive T-cell response on

re-encounter. We are now becoming aware that aging is also associated with a progressive accumulation of apoptotic cells, for there is a progressive impairment in their efficient clearance.



[Adapted from: I am trying to find the paper from which I have "borrowed" this and will reference it once found.]

So, I have condemned the idea that lymphocytes discriminate self-antigen from nonself-antigen to the trash can: I have replaced it with "tidy-demise / messy-demise" discrimination. Furthermore, the aggressive or suppressive instructions on re-encounter can change over time as new naïve T-cells emerge from the bone marrow. It depends on the dominant context of presentation. Every day large numbers of our cells give up the ghost tidily. That means that most epitopes associated with self-cells will have a dominant suppressive action attached to a T-cell's antigen-specific-receptor when it encounters its respective antigen. We can easily overcome this by getting a particular tissue (like nervous tissue, for example) and repeatedly injecting it along with a strongly inflammo-stimulatory cocktail (so called adjuvants). Gradually new T-cells are produced that have not yet been committed to aggression or suppression. Then we end up with an experimental allergic encephalitis. So, attacks on self ***are*** permitted but the conditions for creating them are unusual and need to be persistent. It is my belief that tuberculosis, in particular, deliberately provokes this sort of auto-rejection to provide itself with a suitable culture medium.

At low levels, auto-rejection is probably useful for clearing pockets of disorder. All inflammation includes some level of auto-rejection. But should it get out of control, this will threaten survival and it must be switched off locally. So, a hyper-excited aggressive immune response saturates and turns into focal immunosuppression. It is this sort of environment that allows mutated cells with abnormal growth controls to grow into malignant tumours.

Furthermore, the regenerative phase of inflammation requires invasive stem cells to run rampant in the local area until they reach an appropriate mass and switch off proliferation – so called contact inhibition. Oncogenes result in disruptions to this normal switch off mechanism. These would be no great problem if it were not for the local immunosuppression and a simultaneous disruption around the p53 proteins that are normally sensitive to misbehaved stem cells. Healthy p53 systems can switch them into apoptosis. Macrophages that are not otherwise inhibited are capable of dealing with these abnormal cells.

The focal T-cell tolerance in inflammation is locally expressed and aimed at giving stem cells free reign to do their thing. The inflammatory switch off that follows destructive overzealousness starts locally but spills over systemically. TB, cancer and aging are all accompanied by this. Aging probably results in an increasing prevalence of inflammatory responses that can't close out and so become chronic.

So, is self non-self discrimination dead? No – not at all. It is just nothing to do with thymic T-cells. Every cell in the body has ways to establish who it wants to talk to and co-operate with. Cell adhesion molecules (CAMs) that are all important here and it can hardly be a surprise to find that these molecules are important in immune cell interactions and that T-cell receptors and antibodies are all constructed using of Immunoglobulin super family genes that originated as CAMs. It looks as though the Mhc is deliberately mixing up identities, that would otherwise become a sitting duck for code breaking micro-organisms. Organ specific identities are remarkably conserved in evolution. The addition of a peptide oligomer to the Mhc molecule's groove makes it "look" like an allo-Mhc specificity. That makes it harder to crack the code. But bacteria, in particular, evolve fast and they often have as much as 90 years to play code breaking. I suspect this will prove important in aging.

I've scratched the surface and given some ideas. I have put a bit more in the web file plus some thoughts on philosophical issues. I wish that I could see into your minds to discover what you really want to know about the immune system; I hope that I have made at least a few good guesses.

In conclusion, the lymphocentric immune universe is an assumption that is plain wrong (a hidden assumption). The system is inflammo-centric and this perceptual change is little short of Copernican. So my final act is to paraphrase the original title of my talk (which – by the way – was not my creation).

What gets inflammation up in arms?

And what turns the heat down?

END OF PRESENTATION …….

Notes made during preparation

I made these notes on the way to preparing the talk. You may find some interest here.

(1)
What do we mean when we talk of immunity? In general, most people, immunologists included, are talking about the adaptive immune system of T-cells, B-cells and antibodies and, in particular the T-cells with alpha/beta receptors.

This leaves out various phagocytes, natural killer T-cells, gamma/delta T-cells [which are not Mhc restricted, they have roles in tissue homeostasis] and various other innate lymphocytes. This is one of those distortion things where certain aspects are blown up out of proportion to the whole. The arrival of the alpha/beta style T-cell receptor came late in evolution. My unpublished paper, that I personally take most pride in, points out that, for every immune response to a disrupting agent, the system starts out trying to fix things with the most anciently acquired mechanisms first and it then rolls them out, in the sequence in which they were added during evolution, until they light upon a mechanism that stems the challenge. This means that most challenges do not get as far as using alpha/beta T-cells. ["Flushing out the phlogiston"]

The older ideas, by the way, expect us to accept that alpha/beta T-cells are the commanders of all other immune responses.

(2)
So, who am I and how did I get interested in immunology? This is the brief history:

1976 – I was a Medical Registrar in Neurology at Middlesbrough General Hospital.

Old mantra, "You've got to get your name in print to get on in neurology."
I had near enough zero interest in the stock ideas that were thrown at me.
A doctor phoned and asked me to accept a patient who he thought had Behcet's syndrome and also an anterior spinal artery occlusion. I considered that this was the height of diagnostic kudos and I was very envious.
I became interested in the

- neurological complications of Behcet's syndrome

and of

- multiple sclerosis
- the sero-negative arthritides
- experimental adjuvant arthritis
- experimental meningo-encephalo-myelitis
- the age incidence of cancers and TB and syphilis and the implications for their pathologies
- – of course – immunology

If I was ever to understand this lot, I HAD to learn some immunology.
I didn't progress in neurology
I didn't arrive in print on this until 1995 –19 years later.
I never abandoned the interest.

(3)
So, what authority do I have to appear here and tout my opinion? It certainly doesn't come from universal acclaim. It comes down to provenance and precedence. My writings on this subject were advanced but serially rejected (and thus in the public but not published domain) well before Polly Matzinger's 1994 Danger hypothesis appeared. She proposed "a revolutionary principle on how the (adaptive) immune

system decides what to attack". She rejected the reigning self/non-self assumptions. However, my contributions have remained eclipsed and excluded from general discussion. I suspect that there are active rather than passive reasons for this.

Why are provenance and precedence important? Certainly not to claim credit; that would miss a critical practical point. The strongest justification for claiming provenance is to provide an author with the strongest platform from which to fashion and extend ideas that advance the discipline.

There is comment about this at my web site. Should you be interested, here are four key links that might help you to appreciate how I have arrived here independently; and well before 1994.

- a letter from Neils Jerne dated 1983.
- An article entitled Morphostasis and Immunity dated December 1984
- An article entitled Morphostasis and Immunity, submitted in 1992 and sat upon for seven months before a condemnatory dismissal in March 1993.
- A file on precedence.

Follow these links and you may realise that I owe very little to papers arising from 1994 onwards; and it goes further back if we include the primacy of phagocytes that was resurrected by Charlie Janeway in 1989 (see item (5) below; it was actually Metchnikoff that proposed this – I simply adopted it in 1984).

So this, perhaps, gives me an excuse to make wild stabs at principle.

- The adaptive immune system is **not** denied the right to attack self antigens/components. Inflammation already makes this abundantly clear as attacks of our own cells are common.
- This attack on self can be used to advantage but it must be used with care and transiently. You cannot afford to allow runaway self-destruction to exceed the capacity to regenerate; controls must be in place to inhibit this.
- Intense and prolonged inflammation creates the conditions that could enable self destruction.
- Identity based systems of cell to cell recognition and co-operation are susceptible to having their codes broken – particularly with 70 and more years of exposure to code breakers.
- Damage Associated Membrane Proteins stimulate Toll Like Receptors in "eat me" signals
- The function of MAMPs is probably targeted at this ball park.
- Detritophiles are likely to use this strategy for gaining premium early entry into cells that are on the way out.
- Get in first, beat your opponents, get a head start.
- It doesn't matter if we lose brothers and sisters on the way – they are expendable so long as one of us gets in in the nick of time.
- Here is a paper on DAMPs and TLRs that shows how DAMPs activate TLR receptors.

(4)
I copied this comment from a recent paper,

"Macrophages are cells of the innate immune system that regulate the maintenance of tissue homeostasis, host defence during pathogen infection, and tissue repair in response to tissue injury."

That can be paraphrased into:

"Inflammation is a system that regulates the maintenance of tissue homeostasis, host defence during pathogen infection and tissue repair in response to tissue injury."

. . . . of which the original rendition is a subset. In science certain realisations remain submerged and generally invisible to "scientists" until they are pointed out. Then, as Thomas Kuhn pointed out, *"they may*

… seem very much like tautologies, statements of situations that could not conceivably have been otherwise."

(5)
Charlie Janeway "Approaching the asymptote? Evolution and revolution in immunology"

He is credited with realising the probable primacy of phagocytes in immunology. What he did was to jolt the discipline into realising that it had ignored Metchnikoff's legacy. They had been in hot pursuit of measurable, laboratory based immunology. Remember, immunology is the science of immunology; that is, it is what is currently known about it. As it currently stands, immunology can seem little more than a catalogue of associated interactions. By analogy, it's closer to a train spotters almanac than an exploded simplified overview of the workings of a steam engine. Immunology has a reputation for being notoriously difficult; this is possibly because we are still seeing a distorted homunculus rather than a series of integrated principles in balanced proportions.

(5)
The next person of major influence was the Australian Sir Macfalane Burnet. He wrote a book with a series of prescient comments in the final chapter:

(6)
Evolution and the IS

- If you were to ask me which of my unpublished writings was the most insightful I would chose "Flushing out the phlogiston". This took the ontogeny and phylogeny of immune responses to a fresh level.
- Unpublished: not for the want of trying.
- Unpublished: with rampant rejection
- Rubbished all along the way: perhaps they were justified. I suspect not.
- Metchnikoff set the pioneering realisation of the importance of evolution in fashioning conception.

(7)
Inflammation is a response to any pathogenic stimulus – whether that is a living invader that damages cells and tissues, a physical injury or toxin – or whatever - that disrupts steady state tissue function. If it's a pathogenic stimulus and a particular agent can be identified that causes it (eg, asbestos) then that substance or organism can be awarded with the title a "pathogen". You should note how the tendency to let the extant meaning of pathogen mutate towards "a bacterium, virus, or other microorganism that causes disease" has cold shouldered other injurious stimuli from being awarded the same title; this has distorted its logical meaning.

A lion is invariably a carnivore; a carnivore is not invariably a lion.

Asbestos is a pathogen; a pathogen is necessarily asbestos – it may be a pathogenic micro-organism.

This flow of meaning has done great harm; it has let us lose sight of the point that it is the damage that creates the pathogenic stimulus. This is what triggers an aggressive innate immune response to be rolled out on being re-encountered. Polly Matzinger's 1994 paper latched on to *"danger"* as the precipitant of aggressive adaptive immunity but she regularly (and increasingly) acknowledges that damage is the precipitant. The response to damage is "*post hoc*". "*Danger*" implies some prior knowledge and classification. So I do not use "*danger*" except in acknowledgement that the extant changes in perception

seem destined never to have radiated from my fingertips. "*Danger*" has, however, facilitated the emergence of a fresh, evolving and more enlightening perspective.

(8)
Sanctity of life

- Life is sacrosanct for humans – we hate and avoid its loss and we avoid sacrifice.
- This is not so for our individual cells or for the vast mass of unicellular life.
- It is not so for bacteria - sacrifice is plentiful and used as a technique to propagate.
- It is certainly not so for spermatozoa or ovae.
- The sanctity of life is an emergent peculiarity that becomes manifest in "higher" animals.
- This is probably because they are "complex colonies" with complex, interdependant social structures.
- Skills, knowledge and social behaviour cannot be easily regenerated unless they are an innate attribute of the genome. Their loss can be severe not only to individuals but to groups of them.
- Grief has probably evolved as an advantageous attribute to weld social cohesion and protection.

The sanctity of life is a peculiarity of complex animals that develop skills and social structures and it reaches a zenith in humans. We defend and protect every individual's right to continuing life with increasing vigour – particularly as our societies mature. Globally, this behaviour is a looming catastrophe that has few, if any, ethical solutions. With single cells (and bacteria in particular) overwhelming culls are of little consequence provided that population persistence is maintained. And, similarly, in the human body, for instance, cell death is constant and at a high level. Miscreant or failing cells can easily be sacrificed in a system that is able to easily conjure up healthy "young" replacements. By young I mean cells that are close to the first embryonic divisions after two zygotes created a fertilised ovum. By the time that cells get towards their 50^{th} reproduction their vigour appears to fade and then they fail to communicate effectively with their neighbours (the Hayflick limit) and they eventually apoptose. But this is an actively imposed limit - as many immortal tumour cell lines demonstrate.

(9)
Here's a brief aside. When we give a set of principles a name (very often an acronym) we tend to turn it into a black box. Its innards no longer need examining or exploring. It can be rolled out glibly without checking whether it remains fully justifiable or consistent with extant observations and beliefs. So, "immune system", "pathogen", "PAMPs/MAMPs/DAMPs", "auto-immunity" and so on (and so on), take on an essence that researchers feel comfortable with and believe they understand. It's rather like being comfortable with Fahrenheit then being confronted with a conversion to Centrigrade. The comfort with the old derives from attachment – not logic. We should be able to understand and convert to either immediately (a suitably programmed computer has no problem with this).

Antigen is another. Everyone feels comfortable that they know what this means but it's encumbered with assumed purposes.

Epitope is a less "black boxy" name. It refers to a molecule (usually a protein) that spans some 8 - 22 peptides and can selectively interact with a T-cell receptor or immunoglobin molecule.

(10)
Aside – probably going to axe this – in talk anyway.

- Am I just assuming this or is there something intrinsically "emperor's new clothes" about the way papers are researched and written up?
- Many start out with promising titles but soon get bogged down in lists of interactive biomolecules. Festooned with acronyms; they often end up like little more than a trainspotter's almanac.
- What is so frequently lacking is reaching out for a summative overarching interpretation that leaves out as much detail as possible and emphasises broad principle.

- This is the “this is what you have to grasp” bit.
- You can tuck the “train spotter” details away in the non-essential guts of the article (that is the bits not containing the summative essence) so that the relevant, specialist cognoscenti can validate the details.

(11)
Identity [*awaiting expansion*]

- Identity – is the origin of “immunity”
- Cell adhesion molecules – families – list easily findable
-
- Gap junctions – are they important – does that importance reflect their investigative emphasis?
- Typical pattern of investigative drive – towards a distorted overview
- Hayflick
- Communication and co-operation
- Knowing when to turn off
-

(12)
Observations on aging

- ID based system to established “*what is to be co-operated with*” and “*avoid - or attack - the rest*”
- The identity molecules that command the way that embryonic cells reaggregate after disruption are organ specific and conserved across species. Mix species and you will get organ specific reaggregation including both species. So, this sort of identity is very open to the evolution of mimics and interferers who have cracked the code.
- This is probably why histocompatibility molecules evolved. They are very variable and deliberated jumbled up in each individual of a species.
- The code is still open to code breakers but that takes time – perhaps most of a lifetime of the prospective host. Remember that advantageous bacterial mutations can arise very much faster than a human mutation that can only test the final product out one generation at a time (gametes can test them out faster).
- So, it’s likely that this code cracking is an important part of living with our microbial co-habitees.
- Once you develop a microbial population that finds it easier to hide but still cause damage then there should be a progressive move towards somewhat more intense and certainly more prolonged inflammation.

Aging again

- “Dragging out the rectangle”
- Atheromatous disease – is probably that “normal” consequence of progressive “inflammaging.”
- Intense and or prolonged inflammation favours a shift from peri-venular to peri-arteriolar extravasation then frank arteritis with thrombosis. This goes well with the progressive inflammaging that we see.
- 99% efficient repair leads to progressive deterioration when there are repeated “exposures”
- Identity based system leads to progressive intrusion of mimicking/hidden disruptive invaders

And now, some further random thoughts on aging that may establish aspects of the playing field:

There is some repetition here – my apologies for that.

Inflammation (with the phagocytes that manage it) stands at the hub of organisation in multicellular organisms. Inflammation is, effectively, “king”/”emperor”/”overlord” in this process. All else is subservient and subsidiary. Metazoans that do not have mobile elements can still use elective cell death and either neighbour resorption or neighbour isolation (eg, plants). But let's start with something simple like a sponge as an example of one of our earliest phylogenetic ancestors. These have mobile phagocytic cells that roam the colony keeping things neat and tidy; it’s a sort of inflammation.

Sexual reproduction was lighted upon very early in the history of life on Earth; it is manifest in both plants and animals. Thus, the establishment of this mechanism (of meiosis) predates the metazoan split. The evidence suggests that this occurred 1.2 bn years ago. It was clearly advantageous because it subsequently dominated the majority of metazoan life. Ploidy appeared simultaneously and the haploid to diploid life cycle is the commonest basis for sexual reproduction (though higher ploidy systems do occur – especially in plants). It appears to have been a single emergent event because meiosis is very similar in plants, animals and fungi. Gamete production and meiosis, in these three kingdoms, do not show fundamentally different machinery.

So, what were the advantages of sexual reproduction that made this early and fundamental acquisition emerge? There has been much rumination on this but few solid conclusions. These are some of my thoughts:

(1) Morphostasis/tissue homeostasis is probably heavily involved (note that morphostasis reaches out into more realms than just tissue homeostasis; eg, into metabolic, protein environmental homeostasis and etc, etc).

(2) A return to youthful vigour following gamete fusion is an obvious feature – but is this cause or effect? An example of this vigour is that you don’t find many active 35 year old professional soccer strikers. I noticed at 50 yrs plus that, all of a sudden, I would crash into a 5 bar gate rather than vaulting over it.

The animal form is the vehicle for testing diplotypes. In this phase of the life cycle there is a fairly “low” level of acceptable sacrifice. This has been made lower still by social maturation and maturing ethical norms in the last 70 years).

The gametes are vehicles for testing haplotypes. This includes the maturation and fertilisation of both spermatzoa and ovae. In this phase of the life cycle, MASSIVE sacrifice is acceptable and is practiced. It is probably designed to favour the survival of the “fittest” gamete.

They are a vehicle for testing mutations in the haplotype (diploidy helps suppress deleterious mutations in animal individuals).

(3) Mutation frequencies can be raised in the haplotype so that hopeful monsters can be tested out.

In diploid animals, sexual (preference) selection works strongly in mate preferences for particular hair, skin and eye colour, body shape (and etc). “Ugly” individuals are shunned until there is a population crisis when “hopeful monsters” can grab an enhanced opportunity. Otherwise, mate selection ensures homeostasis of species appearance (hooded and black crows are a good example of sexual preferences – over a 5-10 mile “border” cross breeding does occur but, either side of this border, social “norms” demand mating with just your own style). Similar selective preferences are seen in Hawaian island flies with the newer variants (arising on successive island eruptions) being much less inclined (than their ancestral flies) to mate with variants.

(4) So what’s the mechanism of the return to youthful vigour? I guess that this arrived very early on (like 1 bn years ago). There is, inevitably, a need for the maintenance of order in a colony derived from the fusion of a male-zygote with a female-zygote. Just about everything that was presented in the Methuselah zoom

conference suggests that fidelity of protein maintenance and other parameters declines in an aging clone of cells.

(5) This clonal nature might be very important; I believe that it is. Identity must be established to help cell-to-cell co-operation and to avoid colony infiltration by interlopers. Like friendly aeroplanes/ships etc, there is a code of who to trust and co-operate with and who to avoid or attack. The longer that an individual colony lives, the greater the chances that some organism will learn how to "pick lock" its host's identity algorithms.

Once sexual reproduction has appeared on the scene, the animal phenotype is just a testbed for the species genome. It is probably quite "mindless" of our social commitment to the sanctity of human life except inasmuch as the testbed must survive long enough to fulfil its testing function.

(6) Some thoughts on the origin of self-accumulating/self-constructing chemicals:

There was probably an initial persistence of certain molecules/interactions that were otherwise pitted against a degradation gradient. This probably allowed certain chemical interactions to begin to dominate the local milieu (probably catalytic in some way or another – with energy input favouring particular directions). The earliest of such "persistences" was probably chirality. Chirality, whether left or right-handed, for particular molecules, is a characteristic and very early evolvent in biomolecules. I suspect that this was the first, or one of the first, concentrations of pre-"life" order.

I challenged the idea that disorder is synonymous with entropy in my talk. There's an article in Wikipedia that takes on this mantra. Order - if by that we mean structure, complexity and patterning - is highest in the fractal eddie's that flow as high-availability-energy/low-entropy states "move" towards low-availability-energy/high-entropy states.

So order in a high energy (low entropy) source has lower patterning and complexity (low entropy) than life on Earth. This is constructed/fashioned from the flow of relatively high frequency radiation as it is then degraded to an average 273 degree Kelvin infrared radiation (Earth "sits" in the -60 to +60 centrigrade range, ie, 213- 333 degree Kelvin); this infra-red is a sort of detritus-radiation that's then shipped off (shed) into deep space – never to return. Earth has simply elongated the wavelength of incident solar radiation to lower wavelength radiation. Not much disorder in that – just an energy character change.

So, from chirality, we probably go to simple peptides or even RNA molecules that can catalyze (in analogue versus digital fashion) particular reactions. Chemical persistences have now carried us to the first steps in an ordering process. These can be become complex. Concentration was probably aided early on by micellular lipids in water. These offered both a focal anchor in the lipid membrane and a protected anti-entropic environment.

The *coup de grace* was now to attach peptides to a digital copy coding system that meant that the persistence of successful ordering experiments went from analogue to digital very early on and enabled high-fidelity, long-chain polypeptide construction. Thus, youthful vigour may have arrived long before the sanctity of life even became an advantage. Selective persistence is at the source of both life and evolution. It soon became "persistence" (first) then "evolution" (second) and this was probably first manifest in peptide oligomers or polymers. Folding must have been added in early on.

(7) Now we are set to add in the management of energy sources that turn one form of energy gradient (hot to cold, for example or high frequency to low frequency radiation) to fashion one that's useful inside lipid micelles. That seems universally to have fallen to the energetic nucleotides ATP Etc.

(8) So, youthful vigour appears everywhere in life and depends on exchanges of genetic material. This gives two things;

- probably a genetic patch up repair mechanism
- the potential for genome evolution; genetic cassettes can multiply, diverge and adapt.

So, from the dawn of life genome persistence plus evolution became dominantly important with phenotypic products being mere testing ground vehicles. The phenotypic products are just a vehicle for testing what genome variants best gain selective ("persistence" really) advantages.

The sanctity of Life appeared with the emergence of socially conscious and structured animals. This reached a Zenith in 21st century advanced societies (for example the social emergence of the abolition of death penalties and slavery). With it emerged the drive for prolonging lives.

This is the way society memes are evolving. And, we have now become engrossed in extending our own animal mortality; in a nutshell, "I want to go immortal" quite forgetting the value of rejuvenation by sexual reproduction and the crisis longevity imposes on our planet and our species' long term wellbeing.

(9) "Dragging out the rectangle" to the top right: this link is to my "Other thoughts" section where I discuss this. This implies that, provided that all premature causes of death are avoided, we are destined to die around 92 for males and 95 for females. There is, quite likely, a bell-shaped distribution around 92 (males) and 95 (females), perhaps with uneven tails. Remember that this assumes that all the chance events leading to premature death have been avoided. This leaves us with an inevitable-death-distribution – the moment the machinery wears out – around 95yrs age. The fact that males meet this demise earlier may be a reflection of the haploid nature of a substantial portion of their X-Y chromosome profile.

(10) Remember, inflammation is "king"/"emperor"/"despot". It has a two to four week cycle in which it tries to fix new problems. If it exceeds this, it is forced to recycle and move towards chronic unresolved inflammation. When it can't latch onto a strange epitope, to help it close out this and future similar events, it becomes chronic. Damage and debridement become prolonged. Inflammation must have a feedback cut off to inhibit self tissue destruction that could become life threatening. There is a great 1975 article by Kantor on this and it emphasises that the inflammatory cycle is regularly accompanied by a "tail" of anergy, where delayed type hypersensitivity is (deliberately) suppressed. It dampens down further self destruction. In severe or prolonged inflammation, this phase is prolonged and its effects spill over from local to systemic.

Thus, things like ulcers, weeping breast tumours, that would in all other circumstances have laid us open to fulminating infections and septicaemia are, instead, localised. They are walled off so that, though undesirable, they are very rarely fulminant or immediately life threatening. So, progressively more time is spent in the damage limitation mode of inflammation. Phagocyte function is dampened. In consequence, more apoptotic cells reach bursting point before clearance. These spells of anergy become commoner and more prolonged and are eventually manifest in increasing systemic anergy, inflammaging and fibrosis. (Nb, Nature Immunology has just published an article on "trained immunity" (by which they mean "trained ***innate*** immunity"). Once again, this completely misses the "flashing beacon" that is glaring out at us ("shouting" out) that the adaptive immune arm of our immune system is simply a device to give inflammation a memory: it is the facilitator of "trained innate immunity"and has developed into a highly efficient and evolved state. I find it incredible that immunologists are still so entrapped in the apparent supremacy of adaptive immunity that they "cannot see the wood for the trees". [Perhaps it is really just me who is mad and crackpot.]

(11) Living with our microbiome: First consider the health and vigour of germ-free mice. They are ***less healthy*** and have ***more problems*** than wild mice. So, we are ***adapted*** to live with our microbiome and we mostly benefit from it when young but it's an uneasy relationship as time slips by. *E coli* is an example of this. *E coli* is a major part of our cooperating and useful microbiome but, occasionally, a strain goes rogue (pathogenic). It works out a way to cheat and kill off our own cells rather than wait for the banquet of residual food and sloughing self-cells that are normally supplied to them.

A number of diseases are linked to our microbiome. MHC specific molecules give us an indication of this. HLA B27 is one of the strongest associations with disease and this suggests an identity problem where certain microbes manage to pick-lock our identity codes.

As we heard in the conference multiple individual processes indicate that there is an entropic decay and this leads to increasing disorder. But, remember, this applies to an aging colony; sexual reproduction can set this decay clock back to (or close to) the beginning.