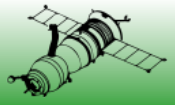
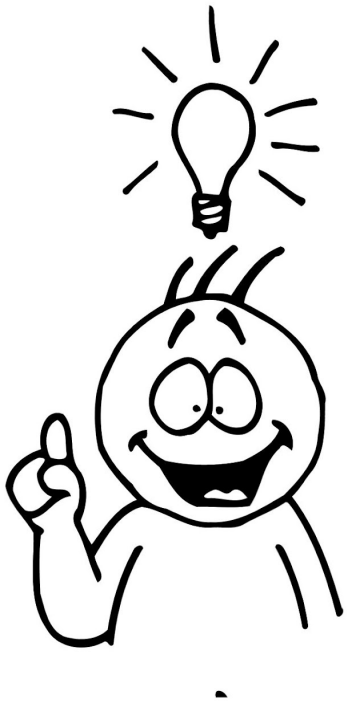
Understanding disease through systems thinking


Understanding



Theory that could help to cure diseases including cancer

Published on December 21, 2004 at 9:18 AM · No Comments

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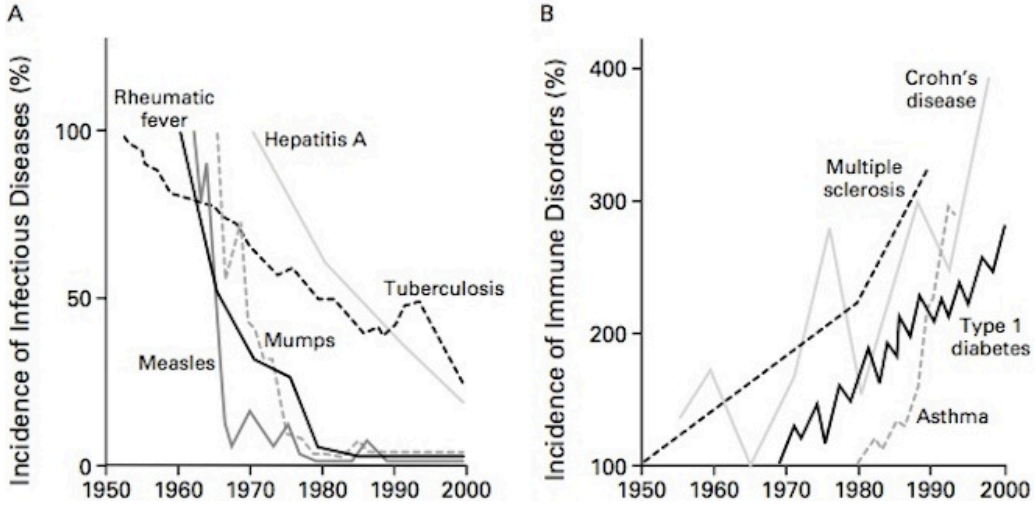
An Open University science student has astonished the world of medicine with a theory that could help to cure diseases including cancer.

The 40-year-old project manager Gary Smith was learning about inflammation as part of an OU course Molecules in Medicine when he struck on a hypothesis so extraordinary that it could have implications for the treatment of almost every inflammatory disease – including Alzheimers, Parkinson's, rheumatoid arthritis and even HIV and AIDS.

His theory is so potentially ground-breaking that it has attracted attention from doctors and medical researchers from as far afield as America, Russia and China.

The news appears in the current issue of sesame, the Open University's new-look magazine for 214,000 Open University around the world.

Today's problems come from yesterday's solutions



Inverse relationship between the incidence of infectious disease (left) and immune disease (right) from 1950 to 2000. (Jean-Francois Bach/NEJM)

Cancer
Alzheimer's
Autoimmune

Infectious diseases

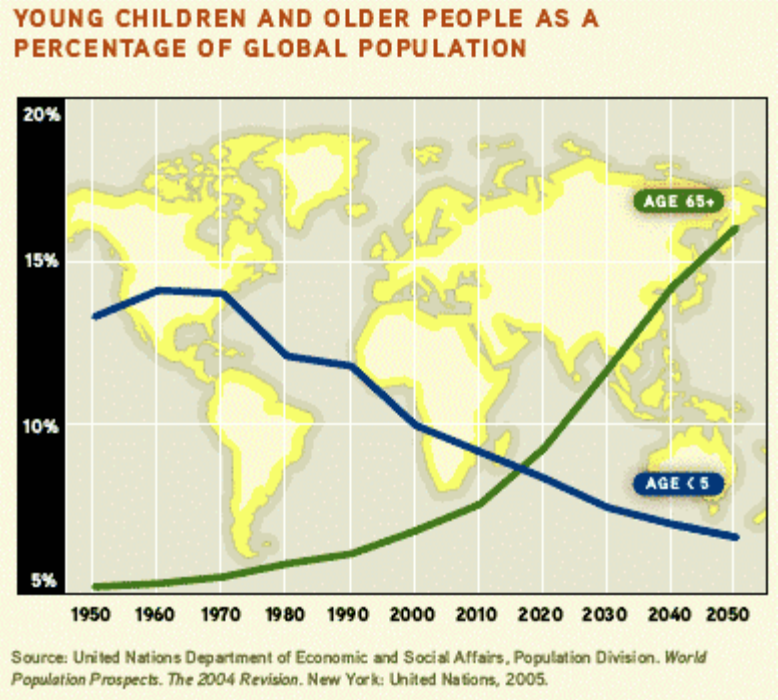
'Cancer overtakes heart disease as number one killer', is the news in The Daily Telegraph.

The Telegraph, and other UK papers, report that a third of people now die from some form of cancer, according to 2011 statistics.

Taking a more glass half-full approach, The Guardian reports that heart deaths have been halved by healthier lifestyles, while conceding that cancers have become the biggest group of killers and that Alzheimer's disease-related deaths are on the increase.

This media barrage of fatal statistics was prompted by the publication of the Office for National Statistics' (ONS) annual report into the number, and causes of, registered deaths in England and Wales during 2011.

Puzzles and complexity



Cancer
Alzheimer's
Autoimmune

Highly complex with multiple causes

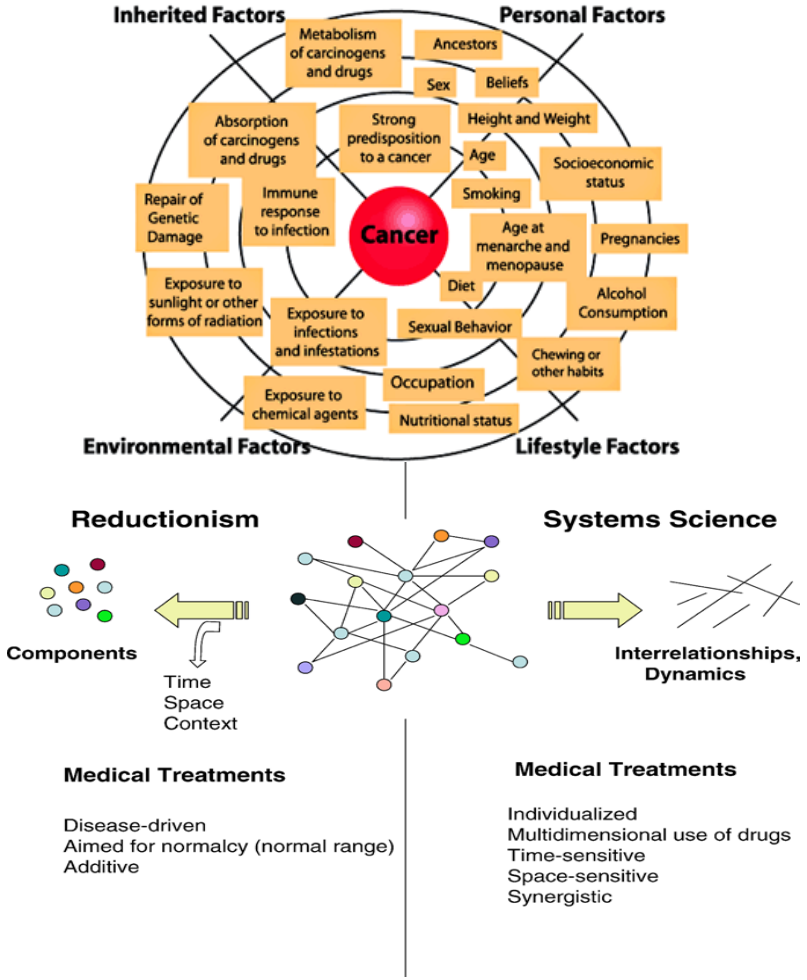
Bacterial
Viral
Fungal

Relatively simple with single cause

Aging is not a common factor for growth in complex diseases

The most immediate factor in considering our current challenges is that we are simply living longer. This makes logical sense when considering cancer and diseases such as Alzheimer's but autoimmune diseases affect mostly the young and middle aged. The problem with autoimmune diseases is that we don't yet fully understand the problem; our current understanding is that the immune system mistakenly attacks the very tissues that it is intended to protect, but we don't really understand the cause (the why) or the process.

Complexity demands new thinking and a fresh approach

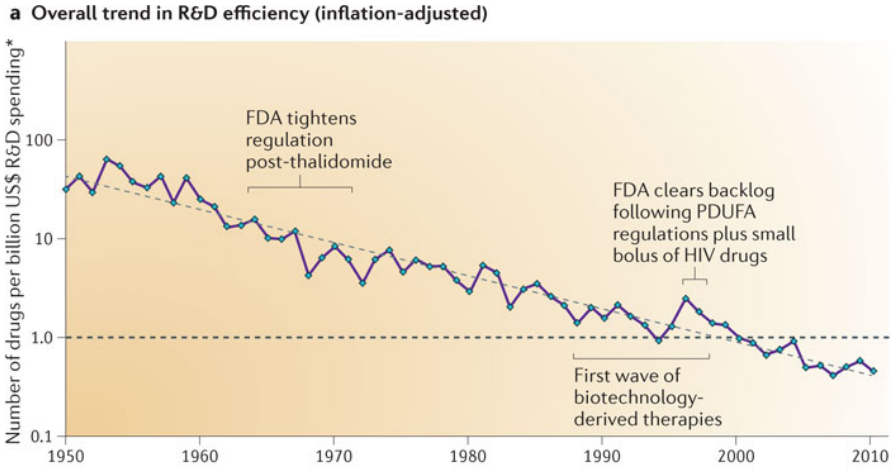


The Clinical Applications of a Systems Approach.
Ahn, Tewari etal. PLoS Medicine 2006.

Has a reductionist approach in medical research and treatment reached its limit?

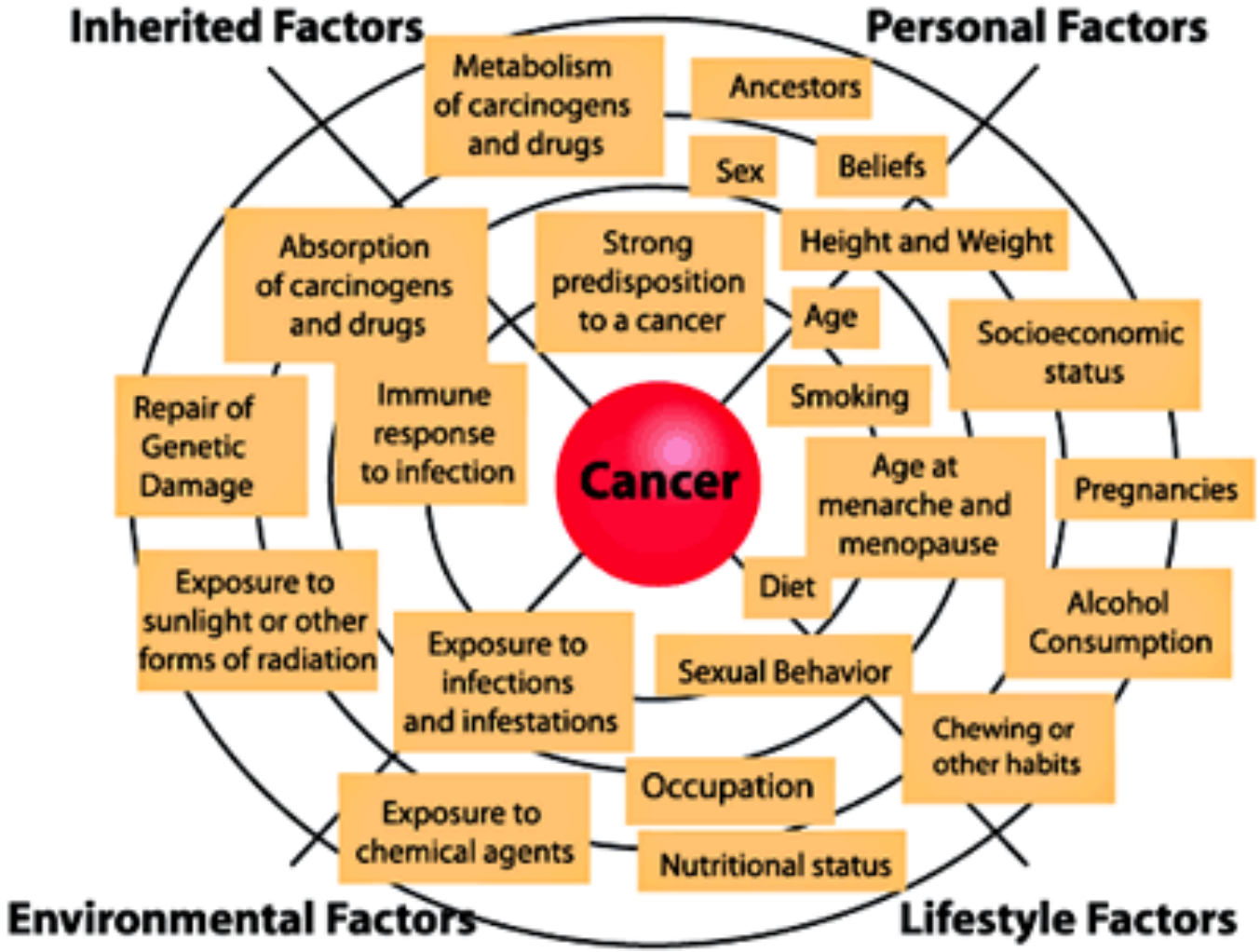
Despite a substantial methodology revolution, the discovery of the human genome and the ascendancy of advanced techniques in biological informatics, the rate of introduction of new drugs into the major worldwide market has declined steadily since the mid 1980s.

Low productivity is not limited to finance or lack of market, budgets have increased 30-fold since the 1970s

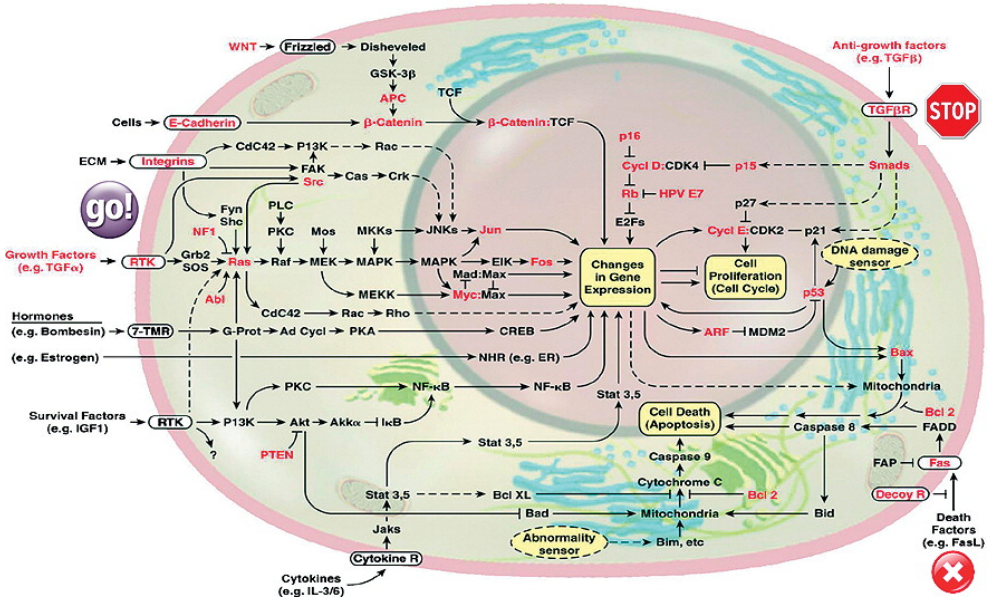


Diagnosing the decline in pharmaceutical R&D efficiency
Jack W. Scannell etal. Nature Reviews Drug Discovery 11, 191-200 (March 2012)

Factors in cancer risk



The cancer paradigm

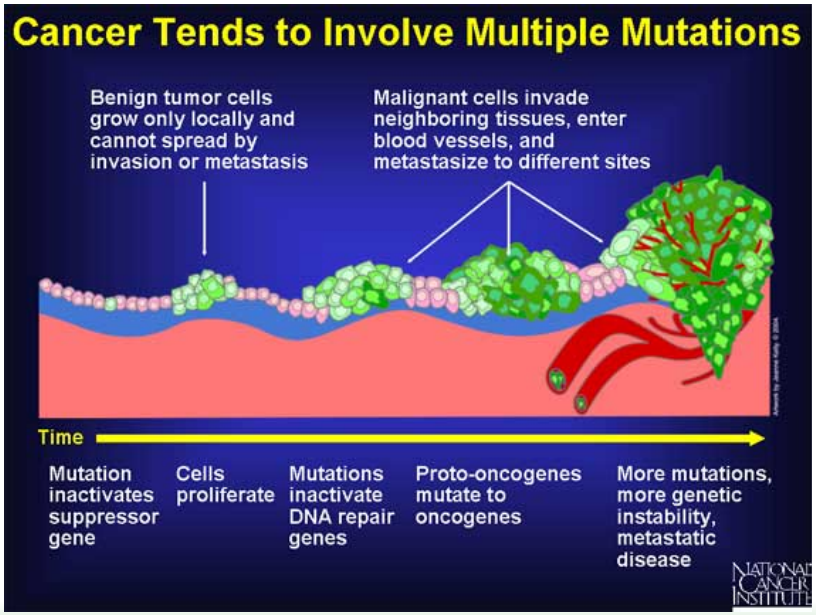


Normal cells cooperate and are tightly regulated by growth controls within their microenvironment.

The development of cancer is a multistage process that arises due to a loss of normal cell control progress.

Within the cell circuitry there are many protective and repair pathways that have to be overcome and there is a lot of redundancy.

This is why cancer is predominantly a disease of aging.



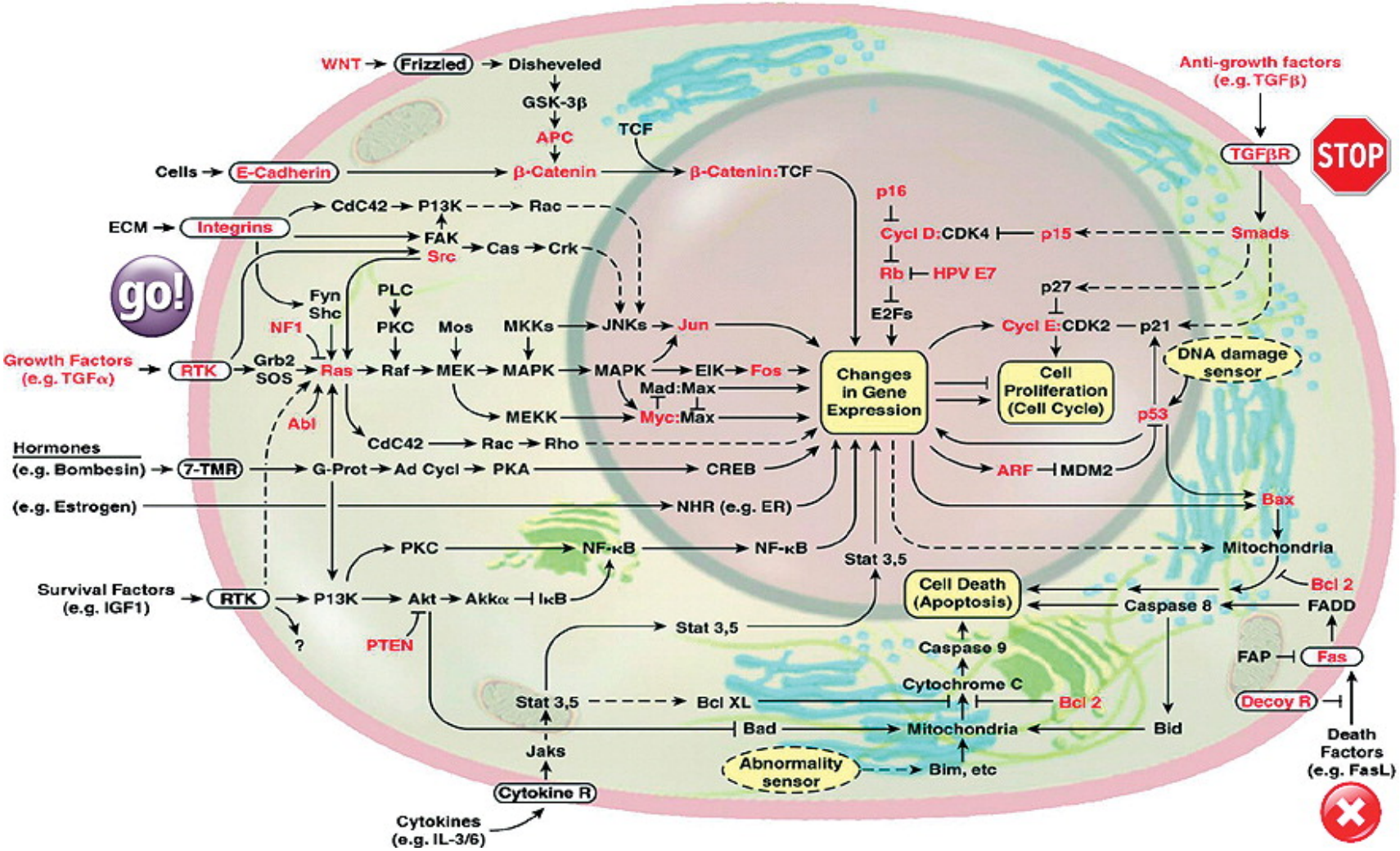
We are in the midst of a revolutionary change in understanding of cancer. However…

The established view is that cancer is actually a plethora of different diseases, all of which have a different blend of mutational causes.

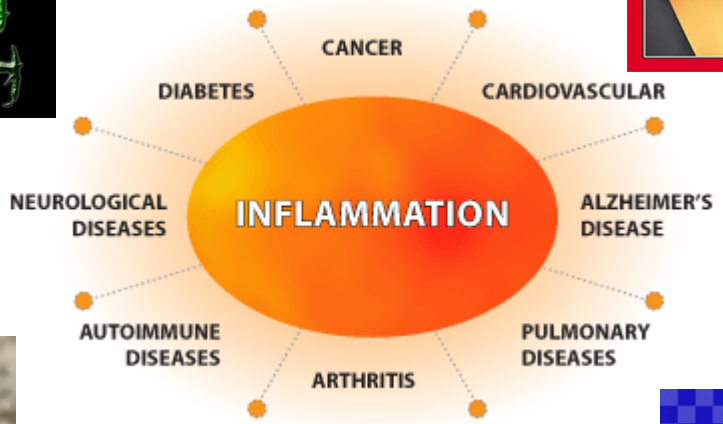
The established view is that the inflammation associated with cancer is a failure of the immune system. “An heroic but unsuccessful attack”.

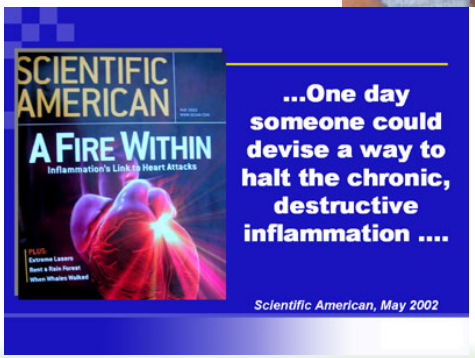
There is a belief that if we understand the individual genetic changes then we can target these and cure the patient.

Failures in the cell circuitry

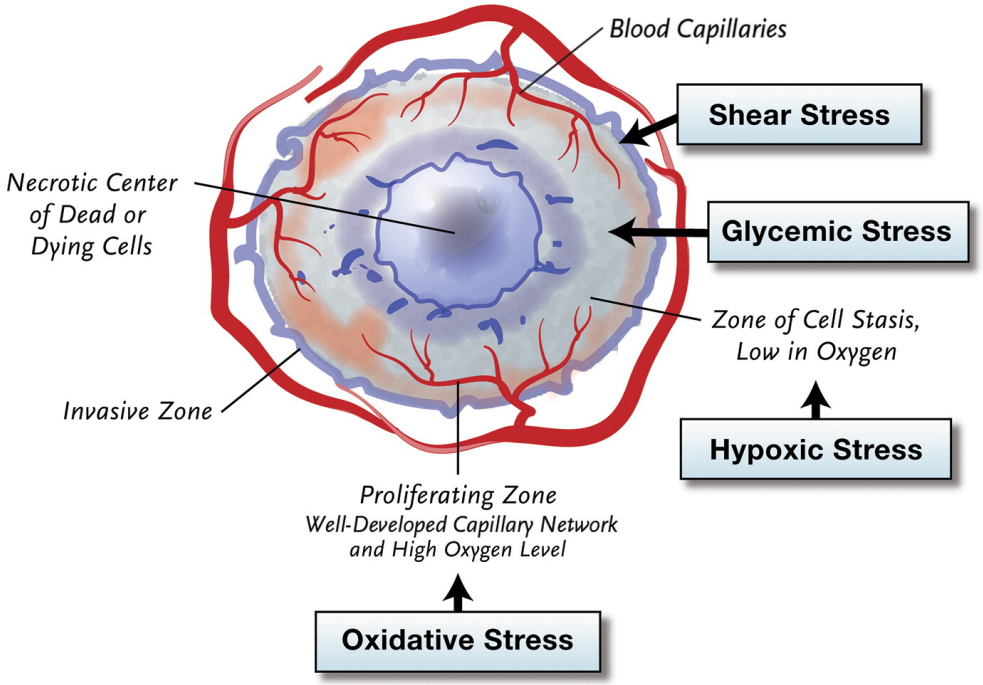


Inflammation – the anomaly





Cancer and its microenvironment



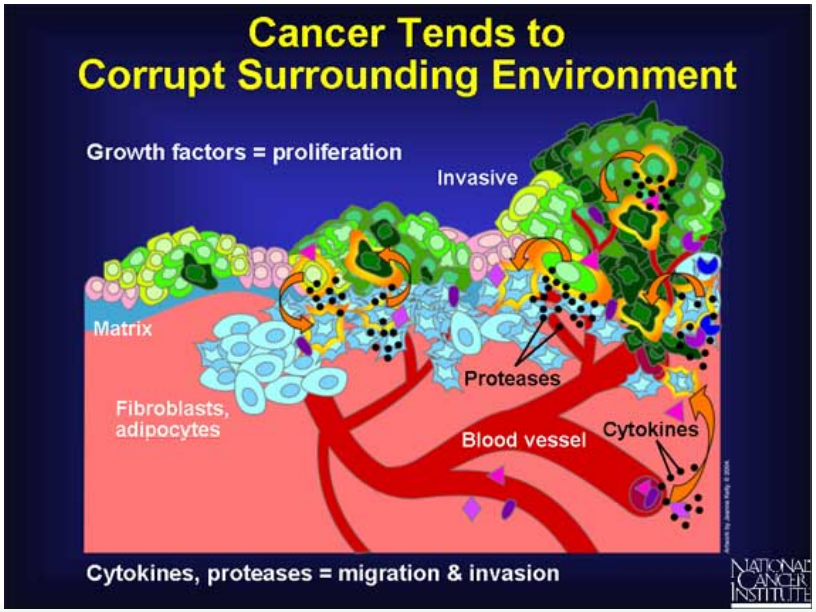
The stress that cancer causes in its microenvironment promotes:
Invasion and migration of cancer to other sites
Angiogenesis (growth of new blood vessels)
Tissue plasticity and remodelling
Death of healthy cells and tissue
Immune Suppression
Further genetic damage and mutation
This activity is a corruption of the normal response to wounding.

Rudolf Virchow is known as "the father of modern pathology". His most recognised accomplishment was his contribution to cell theory:

All living organisms are composed of one or more cells
The cell is the most basic unit of life.
All cells arise from pre-existing, living cells.

In 1863 Virchow noted the remarkable similarity between cancers and wounded tissue. He described "Cancer as the wound that never heals"

Virchow was correct but it has taken 100 years to re-establish this perspective.



The boring old Angiotensin System

INCOSE International Symposium
Las Vegas, NV
June 30 - July 3, 2014

The renin-angiotensin-aldosterone system increases blood volume and pressure

Angiotensin → (**Renin**) → **Angiotensin I** → (**ACE-I** X) → **Angiotensin II** → (**ARB** X)

Direct effects:
- Causes arteries to constrict resulting in an increase in blood pressure.
- Decreases glomerular filtration rate resulting in water retention.
- Increases thirst.

Triggers release of other hormones

Aldosterone

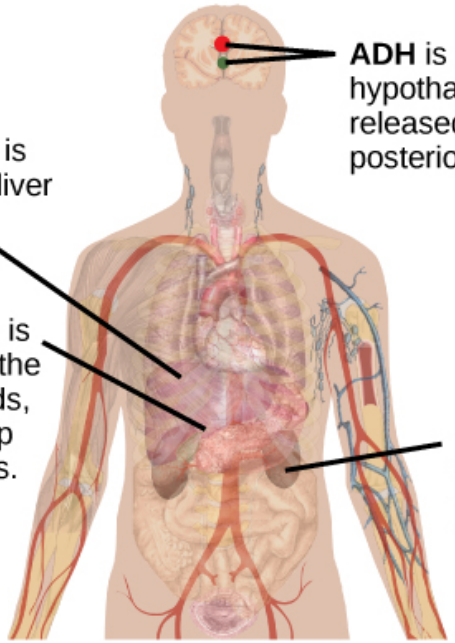
Causes nephron distal tubules to reabsorb more Na^+ and water, which increases blood volume.

ADH

- Mediates insertion of aquaporins into nephron collecting duct cells. As a result, more water is reabsorbed into the blood.
- Causes arteries to constrict.

ANG-II → AT_1 receptor Vasoconstriction

ANG-II → AT_2 receptor Vasodilation

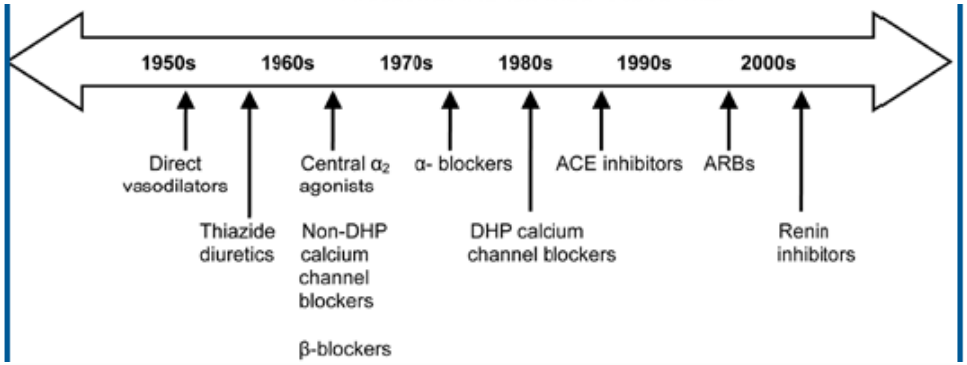


ADH is made in the hypothalamus and released by the posterior pituitary

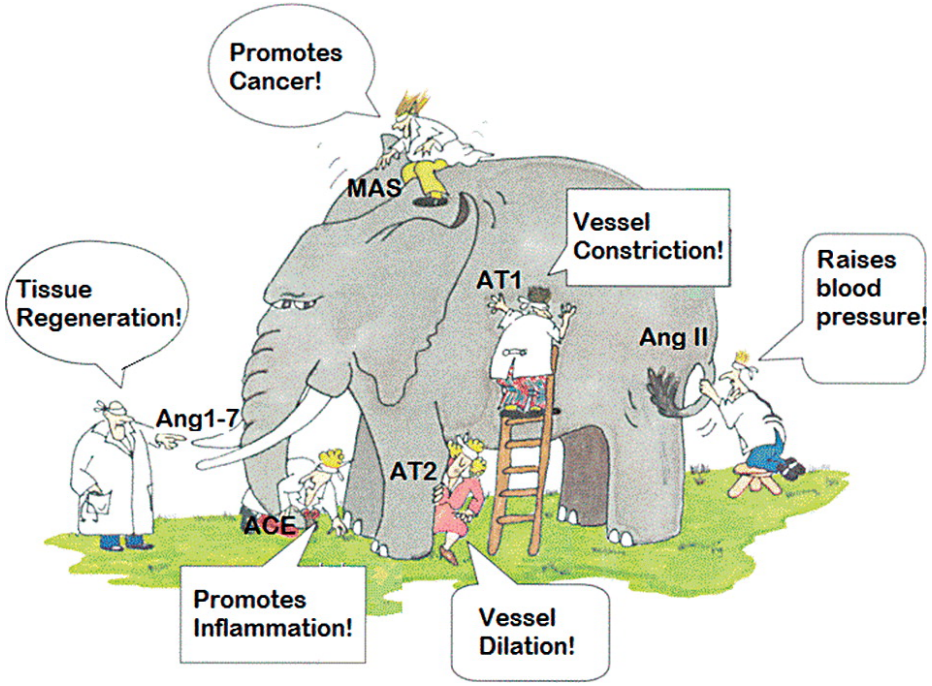
Angiotensin is made by the liver

Aldosterone is produced by the adrenal glands, located on top of the kidneys.

Renin is produced by the kidney.



But.. its not just about blood pressure!



Suzuki Y et al. Inflammation and angiotensin II. Int J Biochem Cell Biol. 2003

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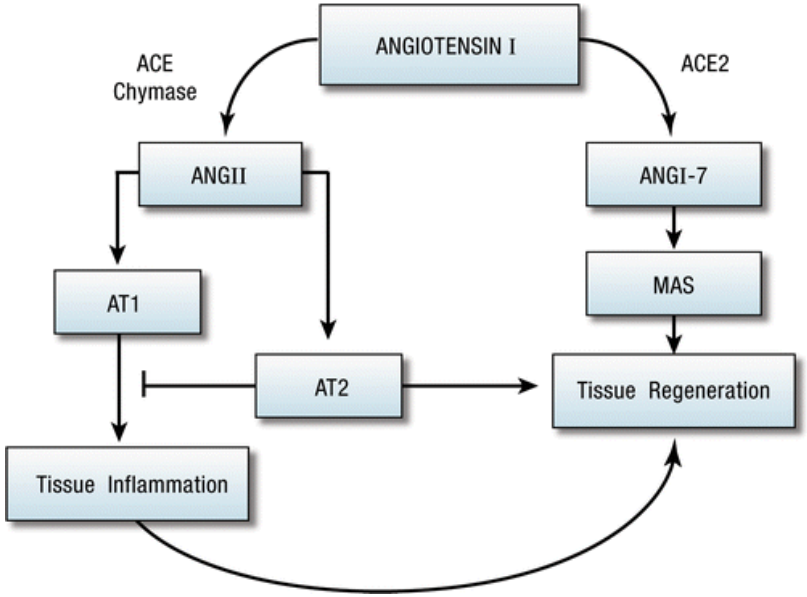
Jadhav SS et al. Effects of combined radiation and burn injury on the renin-angiotensin system. *Wound Repair Regen. 2013*

George AJ , Thomas WG , Hannan RD . The renin-angiotensin system and cancer: **old dog, new tricks**. *Nat Rev Cancer*. 2010

Chappell MC . Emerging evidence for a functional angiotensin-converting enzyme 2-angiotensin-(1-7)-MAS receptor axis**: more than regulation of blood pressure?** *Hypertension*. 2007

Rodgers K , Verco S , Bolton L , Dizerega G . **Accelerated healing** of diabetic wounds by NorLeu(3)-angiotensin (1-7). *Expert Opin Investig Drugs*. 2011



The stress response pathway

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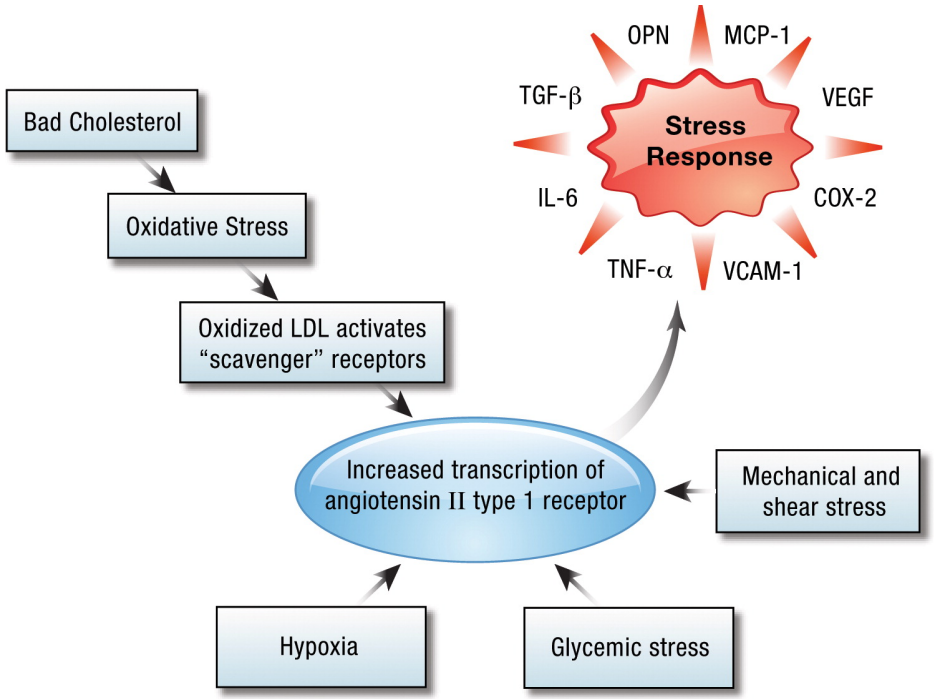


In Cancer, the expression of the Angiotensin system is directly related to the aggressiveness of the disease.

A rapidly growing number of studies and papers have noted the relationship of the Angiotensin system with a great many (and probably all) chronic inflammatory diseases.

Manipulation of both sides of the angiotensin pathway is being explored in these diseases. (but not fast enough)

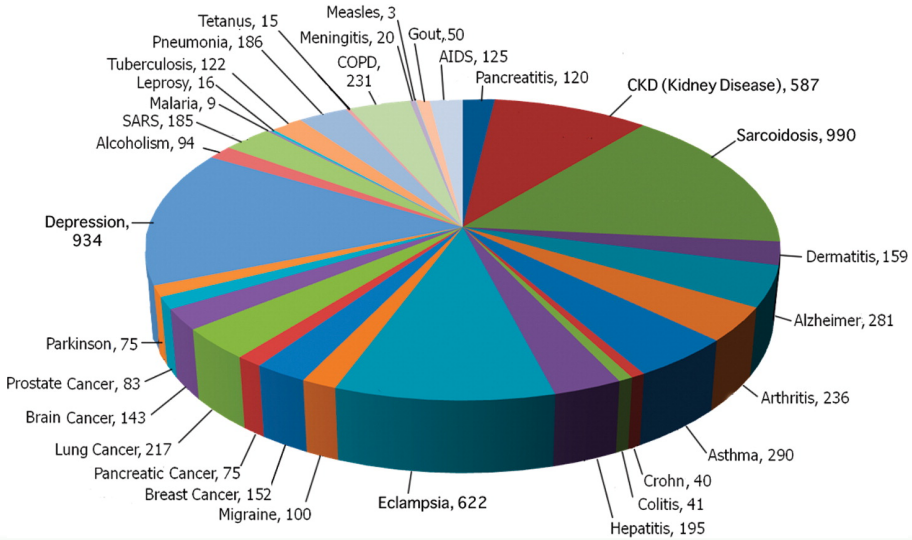
The Angiotensin system is activated by Cell Stress. The purpose of which is intended to resolve or remove the cause of tissue stress through tissue remodelling.

The positive use of the system is evident in wound healing but its misuse is evident in all chronic inflammatory conditions.

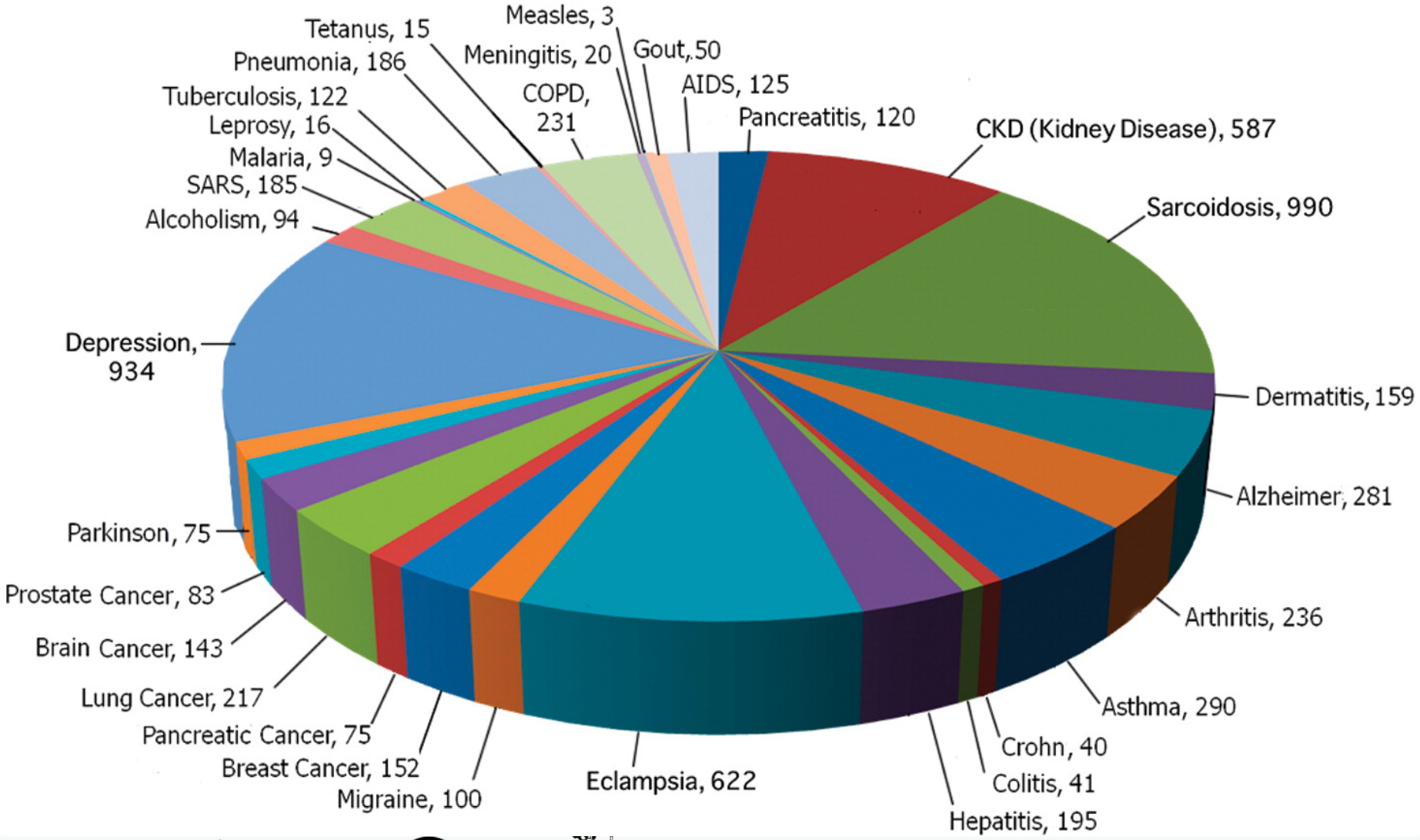
The salt retention and blood pressure effects are simply a small part of the overall function of the system

In Cancer, the unrestrained growth of the tumour results in a stress that cannot be resolved. The wound response itself becomes the driver of malignant processes.

Angiotensin publications in disease (Pubmed 2013)



Pubmed: Angiotensin and disease



A framework to understand disease

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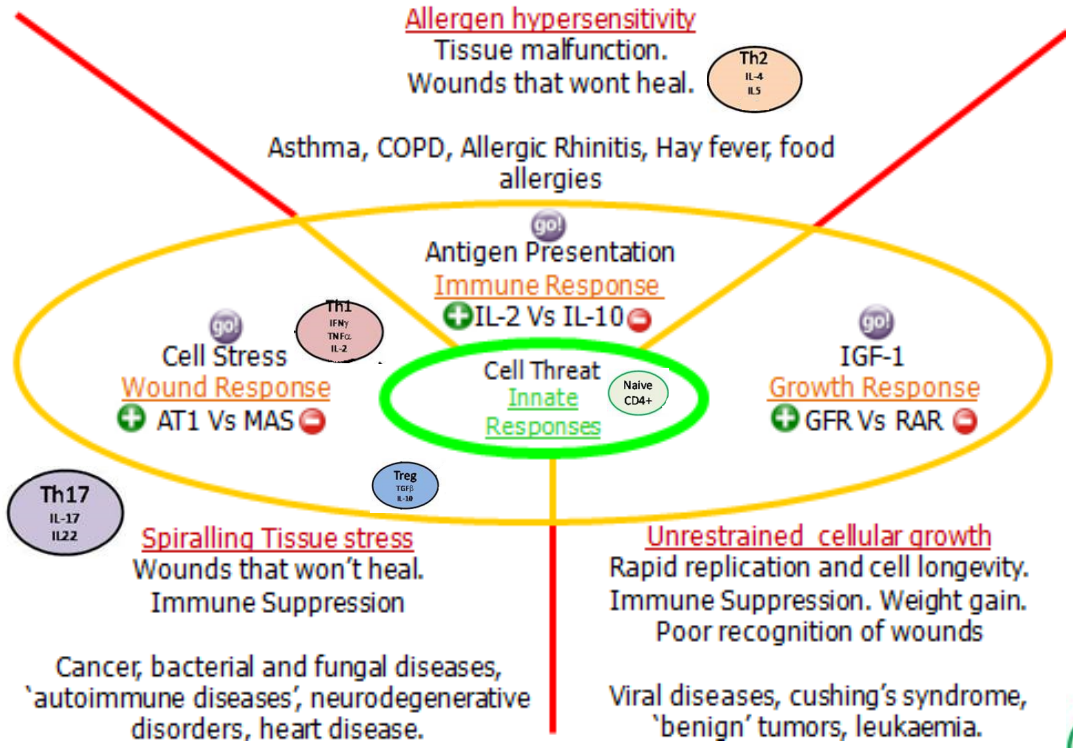
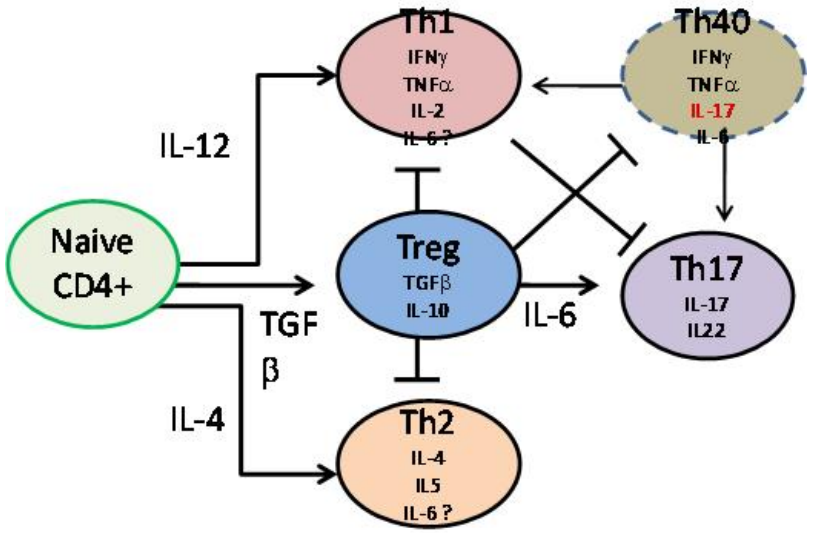


A basic premise for this model is that all cells have multifunctional capabilities. This is of course perhaps most seen in white blood cells, but is also applicable to other cells that are often perceived as more fixed in their activities such as epithelial cells, nerve cells, etc. The model predicts that whilst cells are indeed multifunctional, their degree of focus to a particular response is determined by their environment. In the Cell Response Model, "He who shouts loudest gets the most attention".

In the Cell Response Model, three adaptive responses are envisaged that provide specialist means whereby cells can respond to changes in their environment.

Each of these responses involves a pressure, or force, that drives the response, an accelerator and also a brake for the process. Candidate drivers, accelerators and brakes have been selected based on literature review using Occam's razor (i.e., use the simplest model to explain a phenomenon) and a qualitative "most true associations" approach.

"Established" T Cell thinking

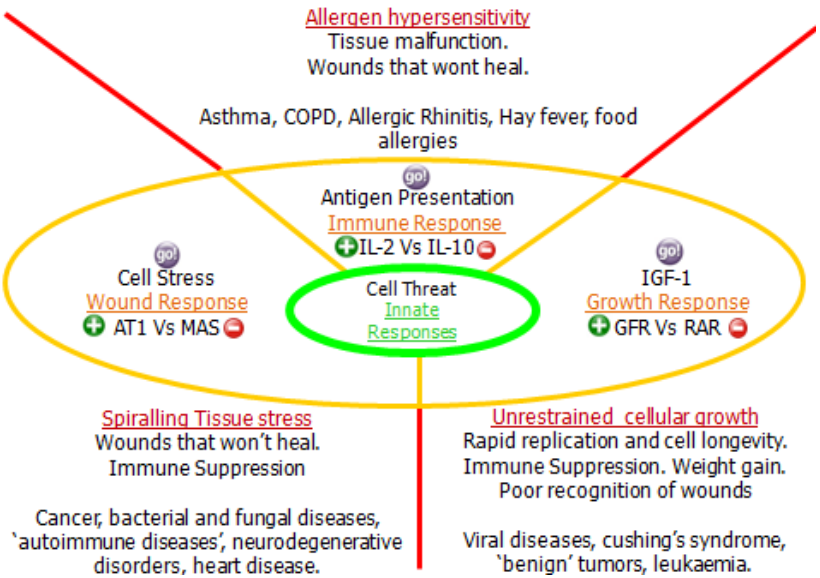


The Role of T Cells in Type 1 Diabetes. By David Wagner

Combinational approaches.

Evolutionary dynamics of cancer in response to targeted combination therapy. **Ivana Bozic et al. Elife. 2013.**

In solid tumors, targeted treatments can lead to dramatic regressions, but responses are often short-lived because resistant cancer cells arise. The major strategy proposed for overcoming resistance is combination therapy. We present a mathematical model describing the evolutionary dynamics of lesions in response to treatment. “The realization of the advantages of simultaneous vs sequential dual therapy will hopefully stimulate efforts to combine agents much earlier in the drug development process.”



Phase-II trial of combination treatment of interferon-α, cimetidine, cyclooxygenase-2 inhibitor and renin-angiotensin-system inhibitor (I-CCA therapy) for advanced renal cell carcinoma. **Tatokoro M et al. Cancer Sci. 2011.**

Fifty-one patients with advanced RCC, an incurable cancer, were treated with this combinational therapy. Complete response was observed in four patients and partial response in seven. None of the four patients who achieved CR relapsed during the 16- to 81-month follow up.

Phase II randomized study of interleukin-2 with or without 13-cis retinoic acid as maintenance therapy in patients with advanced cancer responsive to chemotherapy. **Recchia F. Anticancer Res. 2005**

The study found that low-dose IL-2 and oral RA was more effective than IL-2 alone in improving patient prognosis in a variety of solid tumors, including an increase of lymphocytes and a decrease of angiogenic factors.

Misinterpretation and surprises

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Blood pressure pills 'cancer link'

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Monday June 14 2010

ARBs are used to lower blood pressure

"Blood pressure pills taken by up to one million Britons have been linked to cancer," warned the *Daily Express*. It said that a study has found that patients on the drugs, known as angiotensin receptor blockers (ARBs), were slightly more likely to be diagnosed with the disease than those not taking them.

A well-conducted, well-reported systematic review underpins this report. The study found a modest overall increase in the risk of new cancers in groups of people taking ARBs.

People who are taking ARBs should continue to take them and speak to their GP about any concerns they have. Cancers are rare, and they occurred rarely in these studies. The findings from such research illustrate the difficulty in establishing the balance of benefits and harms for some treatments. ARBs are a well-established and proven treatment for high blood pressure and, therefore, prevent deaths related to cardiovascular disease. This study does not prove that they cause cancer, but the evidence from a well-conducted systematic review suggesting an association with increased risk needs further investigation.

Related Articles

- Blood test for breast cancer 'has potential' (June 27 2014)
- Teens could be given whooping cough booster (June 25 2014)
- Menthol cigs 'encourage teens to smoke more' (June 24 2014)
- Pre-teen girls have 'easy access' to e-cigarettes (June 20 2014)
- Sun tanning 'addictive' suggests study (June 20 2014)

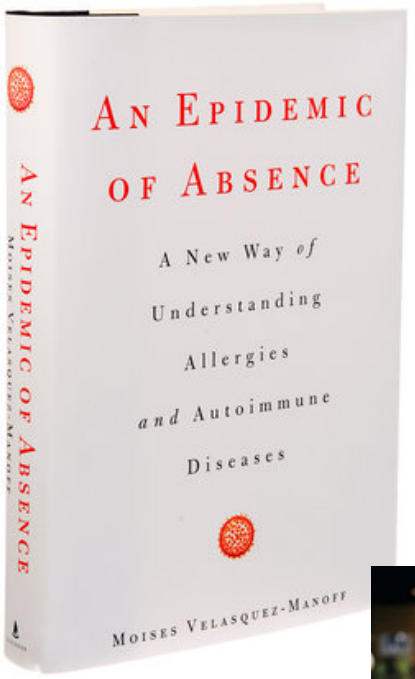
Useful links

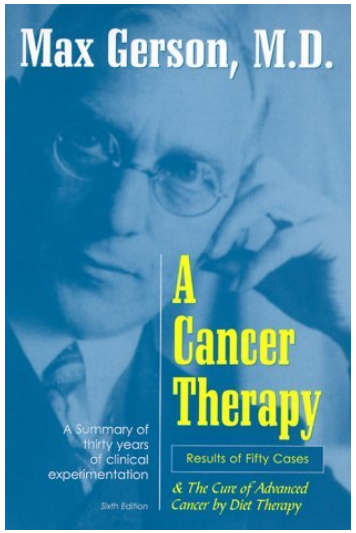
Health A-Z: blood pressure drugs

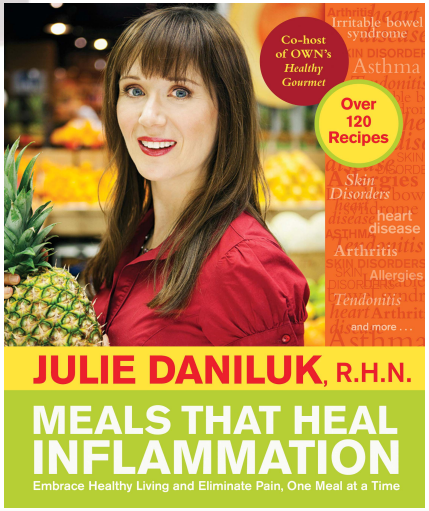
Living with cancer

Information on living with cancer, including treatment, support and different personal experiences of cancer

The even bigger picture!







Final thoughts….

Traditional approaches have failed to explain the nature of our current big problem diseases

Without an understanding of the nature of disease, treatments are likely to remain ineffective and side effects unpredictable

Systems Engineering and Systems Thinking, must not be confined to just engineering.

Reductionism is necessary to understand the components of problems but holistic visualisation and integration are necessary to provide solutions for complex problems

Systems Thinking is a practice which has been discouraged in the medical domain but is growing in importance and recognition

Take up an aspect of research into something different. You never know where it will end up!