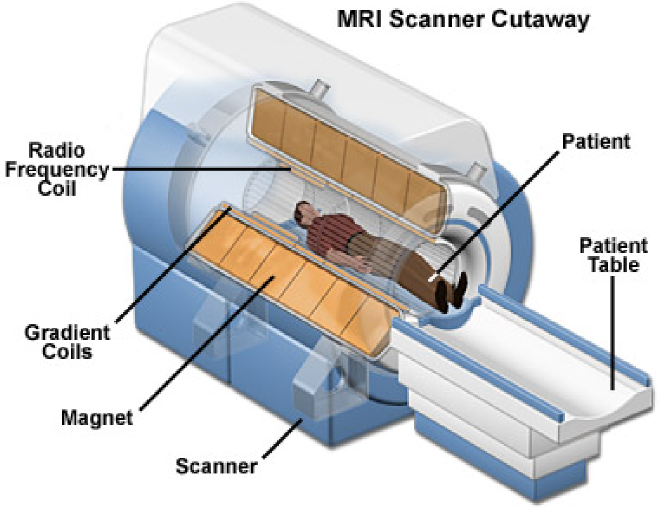
Biomedical Physics

Physics provides medical imaging techniques.

Wilhelm Röntgen, first recipient of the Nobel Prize in Physics

print of Röntgen's first "medical" X-ray, of his wife's hand, taken on December 22, 1895

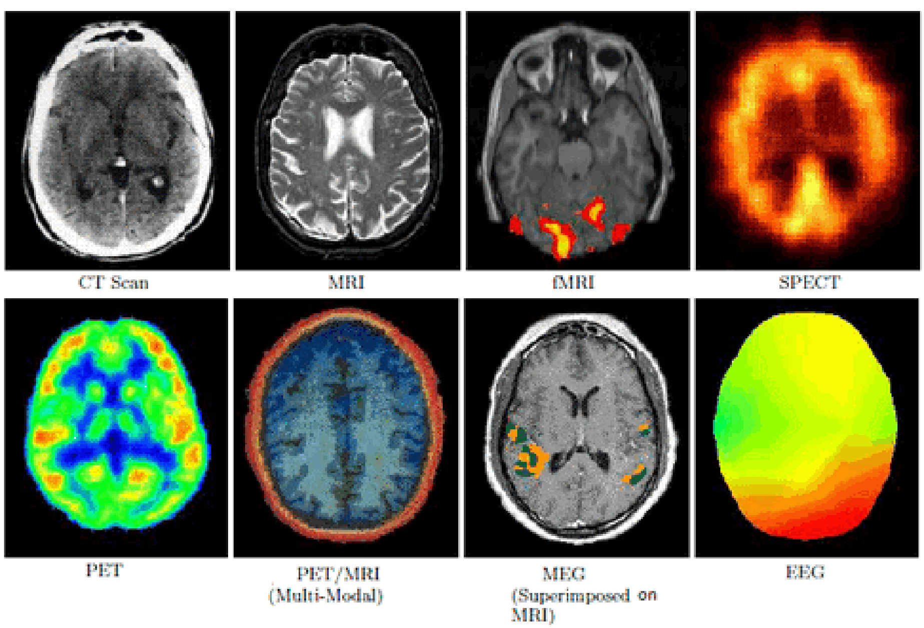
from http://en.wikipedia.org/wiki/X-ray



from http://www.magnet.fsu.edu/education/tutorials/magnetacademy/mri/

ultrasound, 17 weeks

from http://www.pregnancycheck.com/pregnancy-ultrasound.html



brain activity measurements:

EEG, electroencephalography

MEG, magnetoencephalography

PET, positron emission tomography

MRI, magnetic resonance imaging

fMRI, functional magnetic resonance imaging

CT, computer tomography

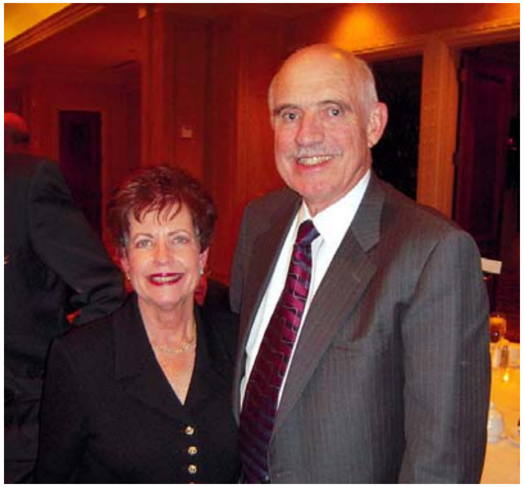
SPECT (single-photon emission computed tomography with gamma-emitting radioisotope)

from http://mazouzbci.net78.net/neurosignal.html

Also fluorescence techniques, atomic force microscopy, etc.

Lasers and optics in medicine and biomedical science: an enormous area

Steven Chu, United States Secretary of Energy
Nobel Prize for Physics (1997)
professor of physics; professor of molecular and cell biology
quantum optics, general relativity;
single molecule biology, biophysics, and biomedicine

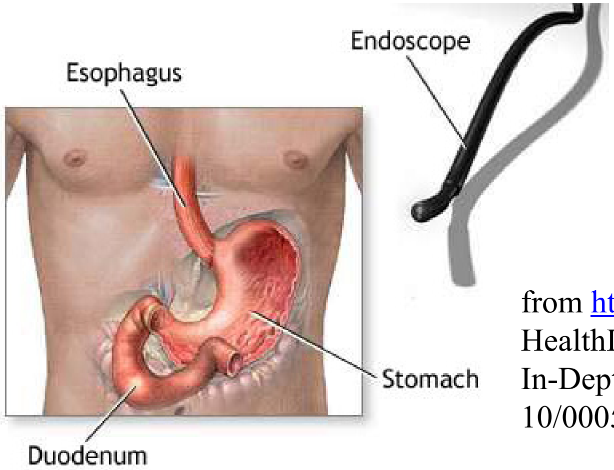


Charles Munnerlyn, cofounder of VISX, with his wife Judy.

By 2002, about two thirds of laser vision correction procedures in the U.S. were performed with VISX equipment.

His degrees are in physics and optics, from Texas A&M and Rochester. He has also been an avid amateur astronomer since age 13.

from http://en.wikipedia.org/wiki/Charles_Munnerlyn



from http://health.rush.edu/HealthInformation/In-Depth Reports/10/000588.aspx

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Nuclear medicine is also an enormous area, for imaging and treatment.

Nanotechnology: another level of imaging, drug delivery, etc.

Table 1: A Partial Nanomedicine Technologies Taxonomy [5]

Raw nanomaterials	**Cell simulations and cell diagnostics**	**Biological research**
Nanoparticle coatings	Cell chips,	Nanobiology
Nanocrystalline materials	Cell stimulator	Nanoscience in life sciences
Nanostructured materials	**DNA manipulation, sequencing,**	Drug delivery
Cyclic peptides	**diagnostics**	Drug discovery
Dendrimers	Genetic testing	Biopharmaceutics
Detoxification agents	DNA microarrays	Drug encapsulation
Drug encapsulation	Ultrafast DNA sequencing	Smart drugs
Fullerenes	DNA manipulation and control	**Molecular medicine**
Functional drug carriers Smart drugs	**Tools and diagnostics**	Genetic therapy
MRI scanning (nanoparticles)	Bacterial detection systems	Pharmacogenomics
Nanobarcodes	Biochips	**Artificial enzymes and enzyme control**
Molecular medicine	Biomolecular imaging	Enzyme manipulation and control
Nanoemulsions	Biosensors and biodetection	**Nanotherapeutics**
Nanofibers	**Diagnostic and defense applications**	Antibacterial and antiviral nanoparticles
Nanoparticles	Endoscopic robots and microscopes	Fullerene-based pharmaceuticals
Nanoshells	Fullerene-based sensors	Photodynamic therapy
Carbon nanotubes	Imaging (cellular, etc.)	Radiopharmaceuticals
Noncarbon nanotubes	Monitoring	**Synthetic biology and early nanodevices**
Quantum dots	Lab on achip	Dynamic nanoplatform nanosome
Artificial binding sites	Nanosensors	Tecto-dendrimers
Artificial antibodies	Point of care diagnostics	Artificial cells and liposomes
Artificial enzymes	Protein microarrays	Polymeric micelles and polymersomes
Artificial receptors	Scanning probe microscopy	**Biotechnology and biorobotics**
Molecularly imprinted polymers	Intracellular devices	Biologic viral therapy
Control of surfaces		Virus-based hybrids
Artificial surfaces-adhesives	Intracellular biocomputers	Stem cells and cloning
Artificial surfaces—nonadhesive	Intracellular sensors/reporters	Tissue engineering
Artificial surfaces—regulated	Implants inside cells	Artificial organs
Biocompatible surfaces		Nanobiotechnology
Biofilm suppression	BioMEMS	Biorobotics and biobots
Engineered surfaces		
Pattern surfaces (contact guidance)	Implantable materials and devices	Nanorobotics
Thin-film coatings	Implanted bioMEMS, chips, and electrodes	DNA-based devices and nanorobots
	MEMS/Nanomaterials-based prosthetics	Diamond-based nanorobots
Nanopores	Sensory aids (artificial retina, etc.)	Cell repair devices
Immunoisolation	Microarrays	
Molecular sieves and channels	Microcantilever-based sensors	
Nanofiltration membranes	Microfluidics	
Separations	Microneedles	
	Medical MEMS	
	MEMS surgical devices	

from Moni Saha, "Nanomedicine, A Review", http://www.omjournal.org/ReviewArticle/FullText/200910/FT_Nanomedicine.html

The chemists also have something to say.

From http://www.guardian.co.uk/science/2012/oct/09/nobel-prize-chemistry-2012-live

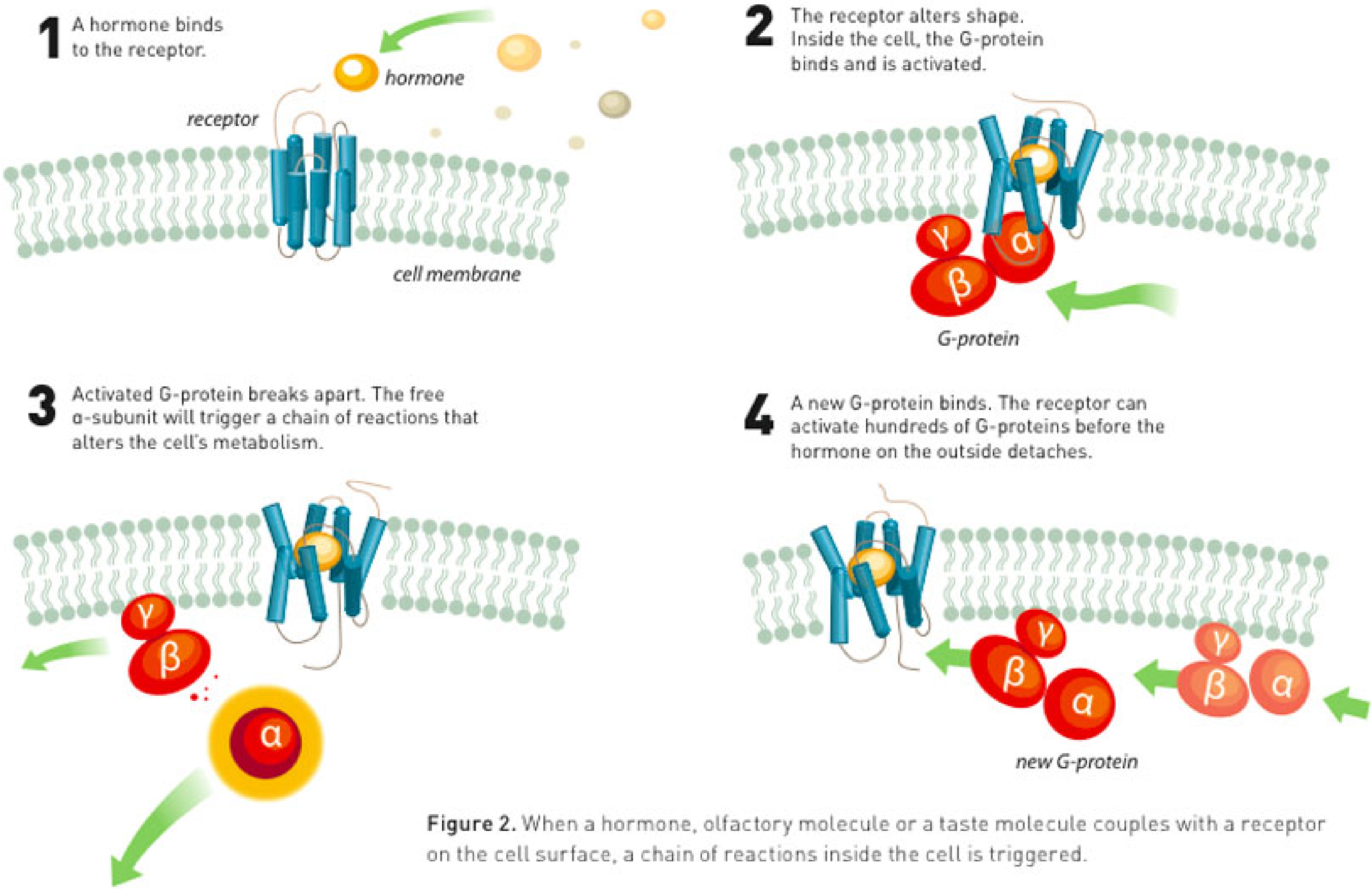


Figure 2. When a hormone, olfactory molecule or a taste molecule couples with a receptor on the cell surface, a chain of reactions inside the cell is triggered.

http://news.discovery.com/human/nobel-prize-chemistry-121010.html

What about theory?

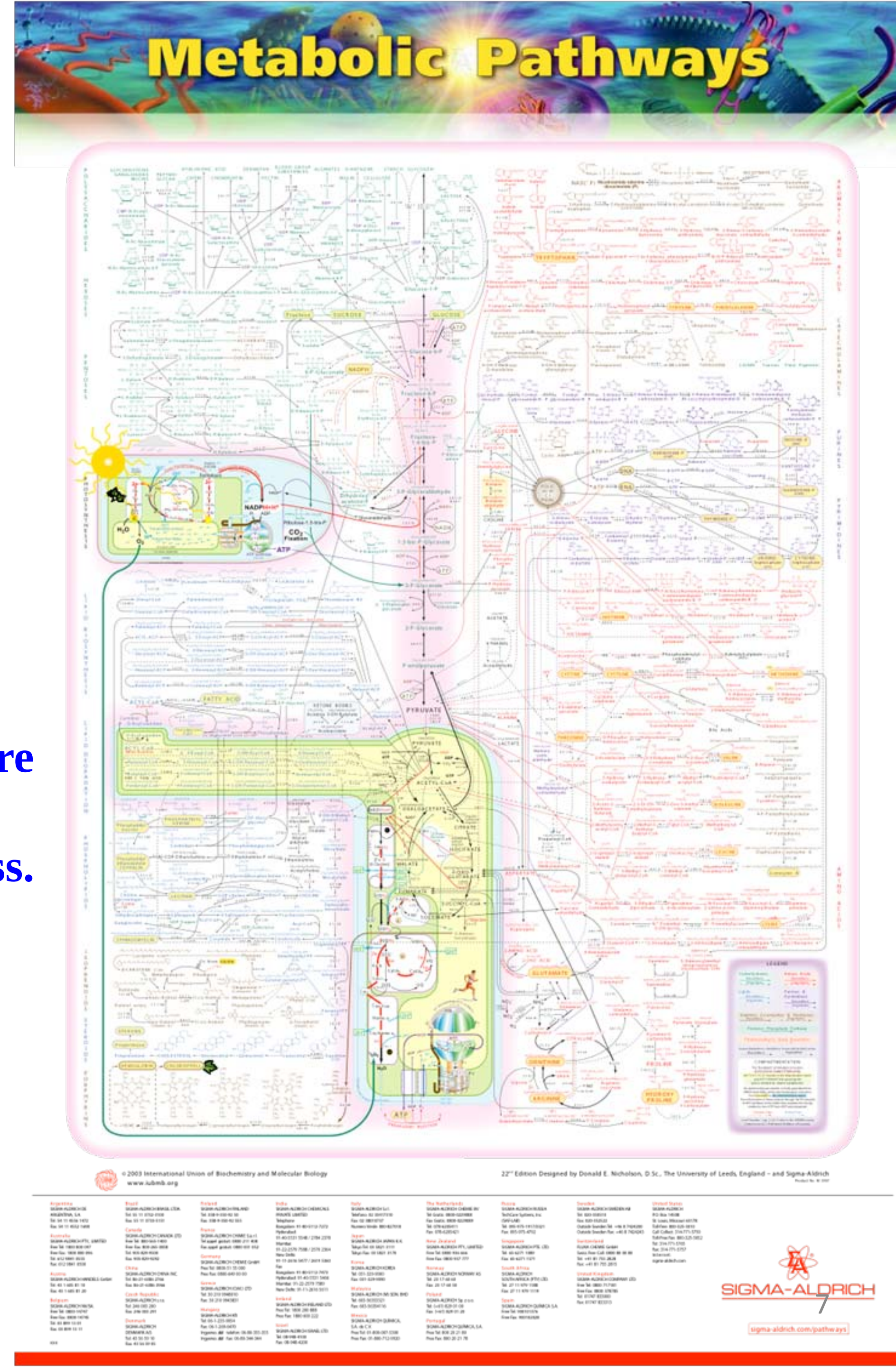
One dream for the future:

Set up and solve the N coupled equations for the most relevant dx_k/dt , where x_k is the concentration of a specific biochemical molecule in a specific region, and dx_k/dt is its rate of change.

But large-scale quantitative simulations will be an enormous task for a world-wide community, with N ~ 100, 1000, or much more for significant problems, even after they are drastically reduced with maximum cleverness.

The hardest part will be getting reliable parameters, such as reaction rates.

Note that the pathways for various processes and diseases (e.g. cancers, heart diseases, and diabetes) are sure to be rather strongly coupled.



The principal paradigm of how to simplify the equations: Michaelis–Menten kinetics (1913)

$$E + S \underset{k_r}{\overset{k_f}{\rightleftharpoons}} ES \xrightarrow{k_{cat}} E + P$$

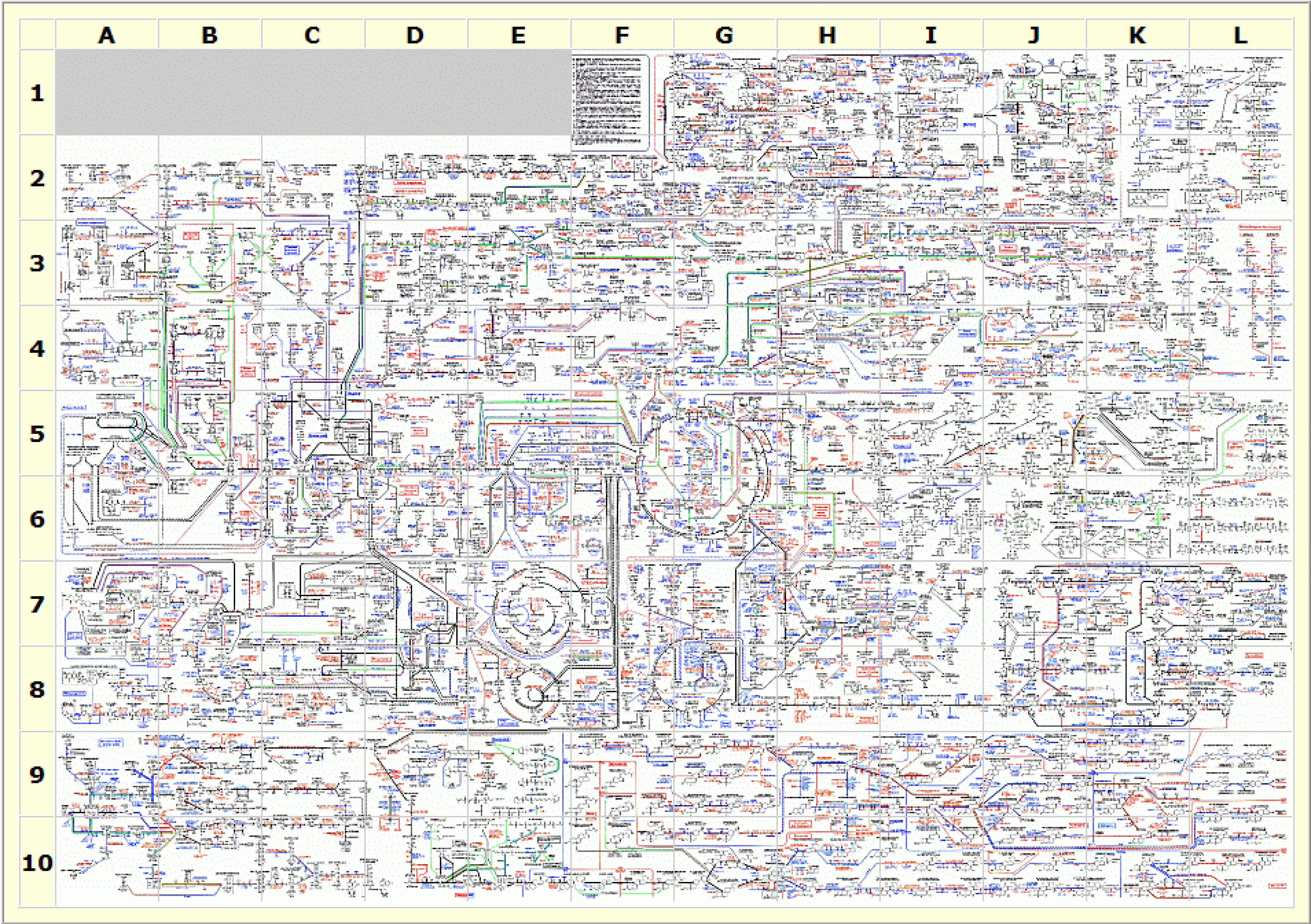
The enzyme E catalyzes the reaction to substrate product P, and the reaction rate increases with substrate concentration S.

German biochemist Leonor Michaelis

Canadian physician Maud Menten

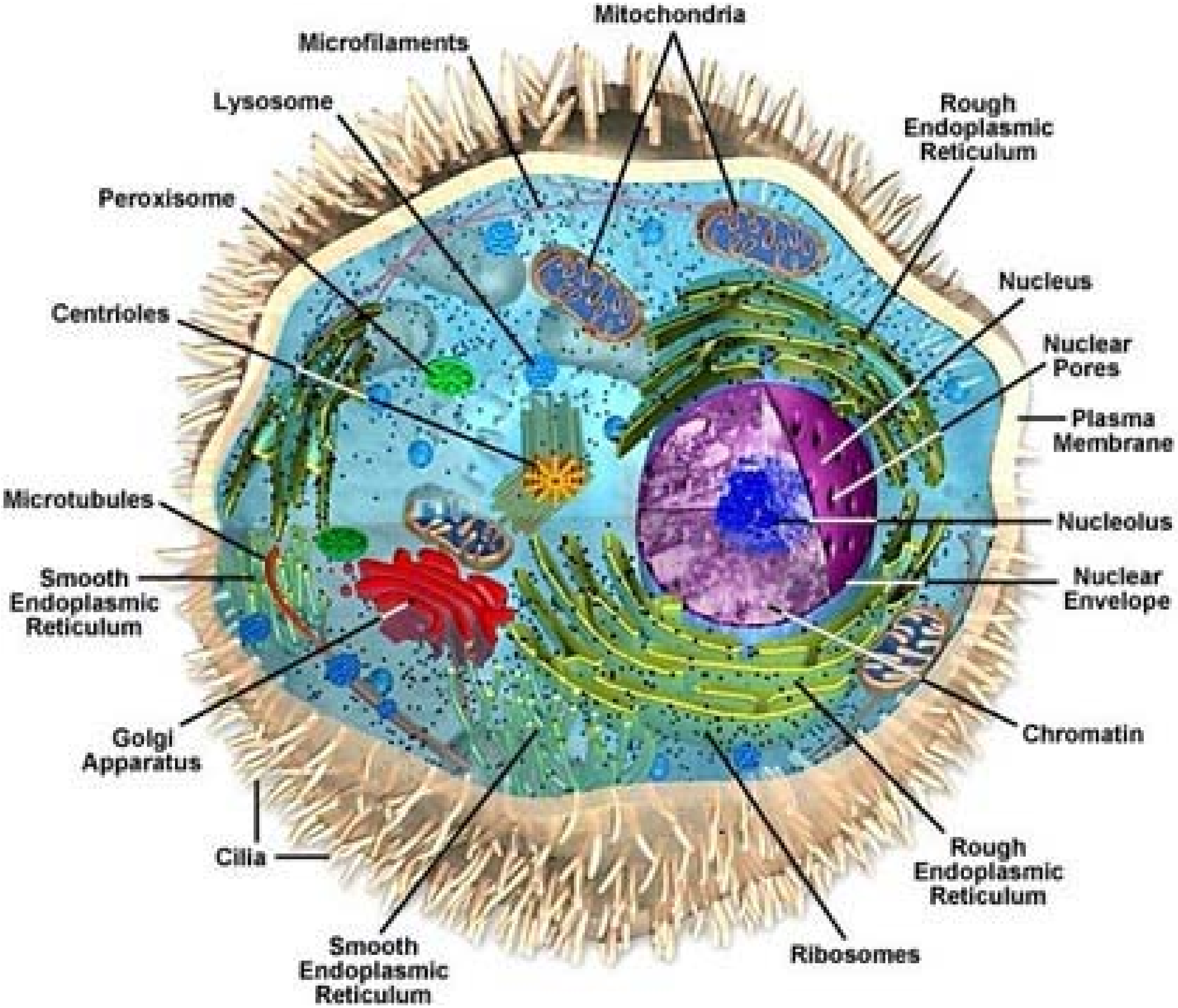
from http://en.wikipedia.org/wiki/Michaelis–Menten_kinetics

But the coupled equations for all relevant pathways are still enormously complicated, even at this "mesoscopic" level.



from http://www.uz.zgora.pl/~jleluk/animacje/show_thumbnails.pl.htm

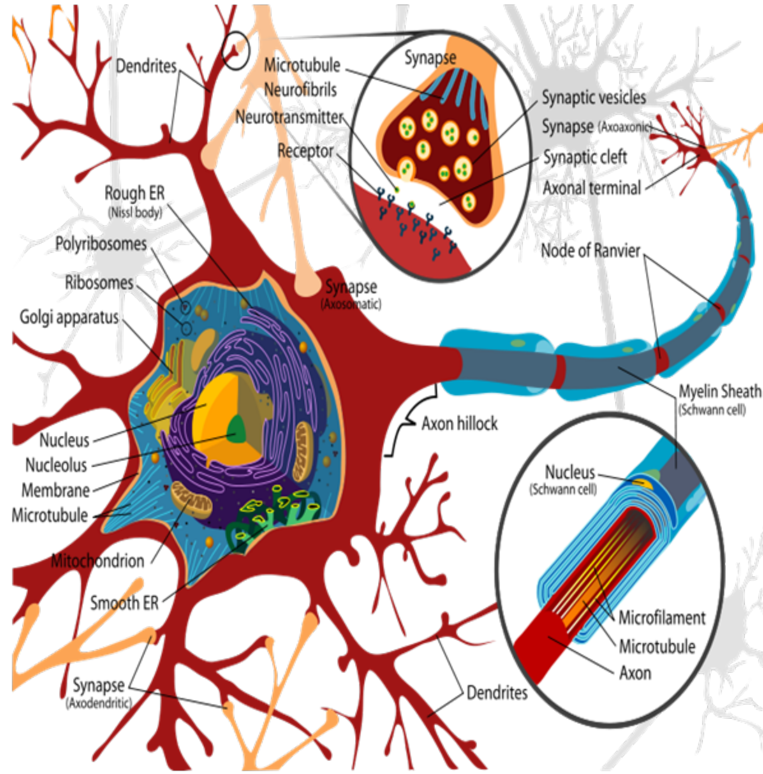
Every cell is complicated, and miraculous in its performance.



from http://www.mcb.ucdavis.edu/

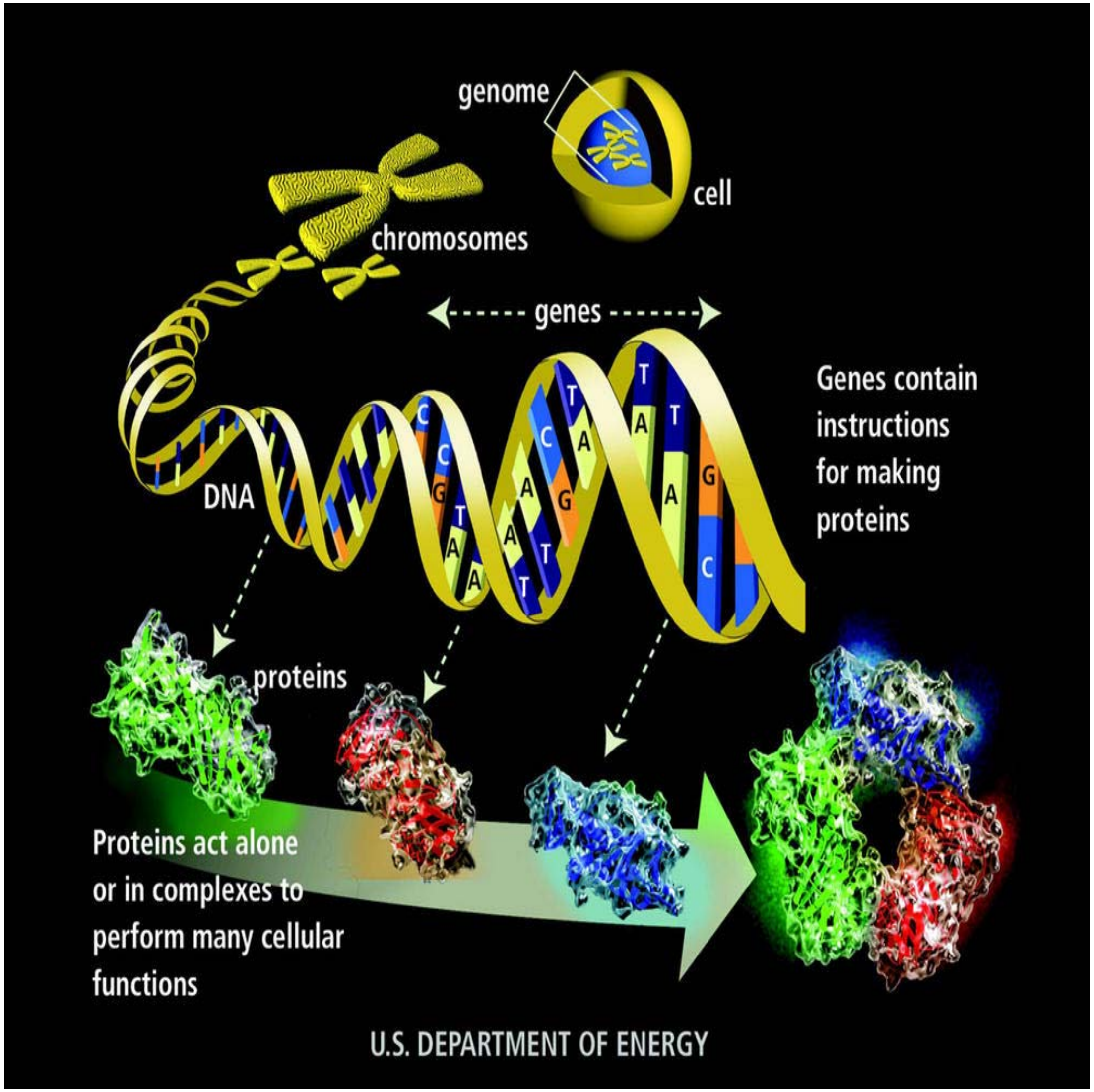
Your body has trillions of cells, of many different kinds in many different organs, each performing incredibly sophisticated functions on short time and length scales.

from http://www.3dscience.com/Resources/3d_Human_Anatomy.php



from http://emedtravel.wordpress.com/2012/06/25/how-neurons-pass-signals-through-the-nervous-system/

The most simplistic view: Signaling molecules trigger a change in gene expression, so that proteins are ultimately produced. But the reality is vastly more complex.



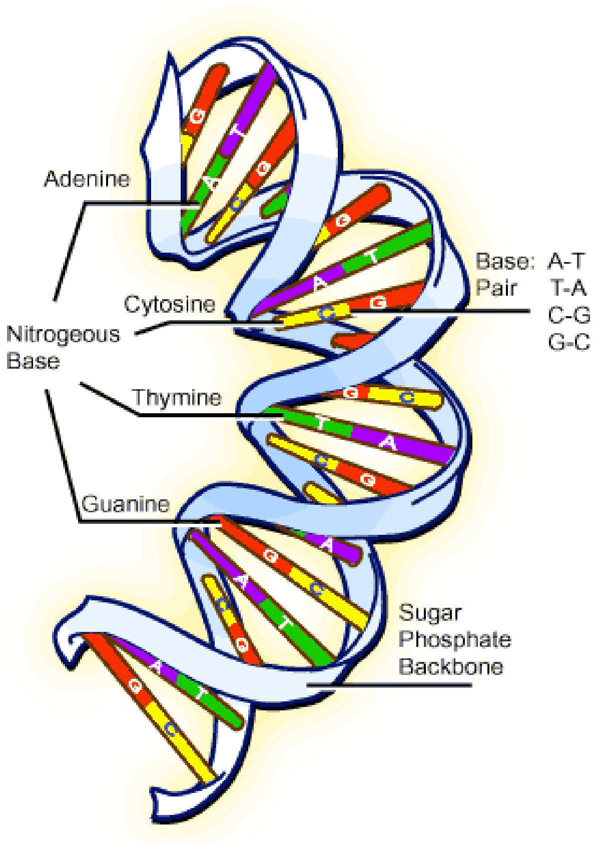
from http://www.broadinstitute.org/education/glossary/genome

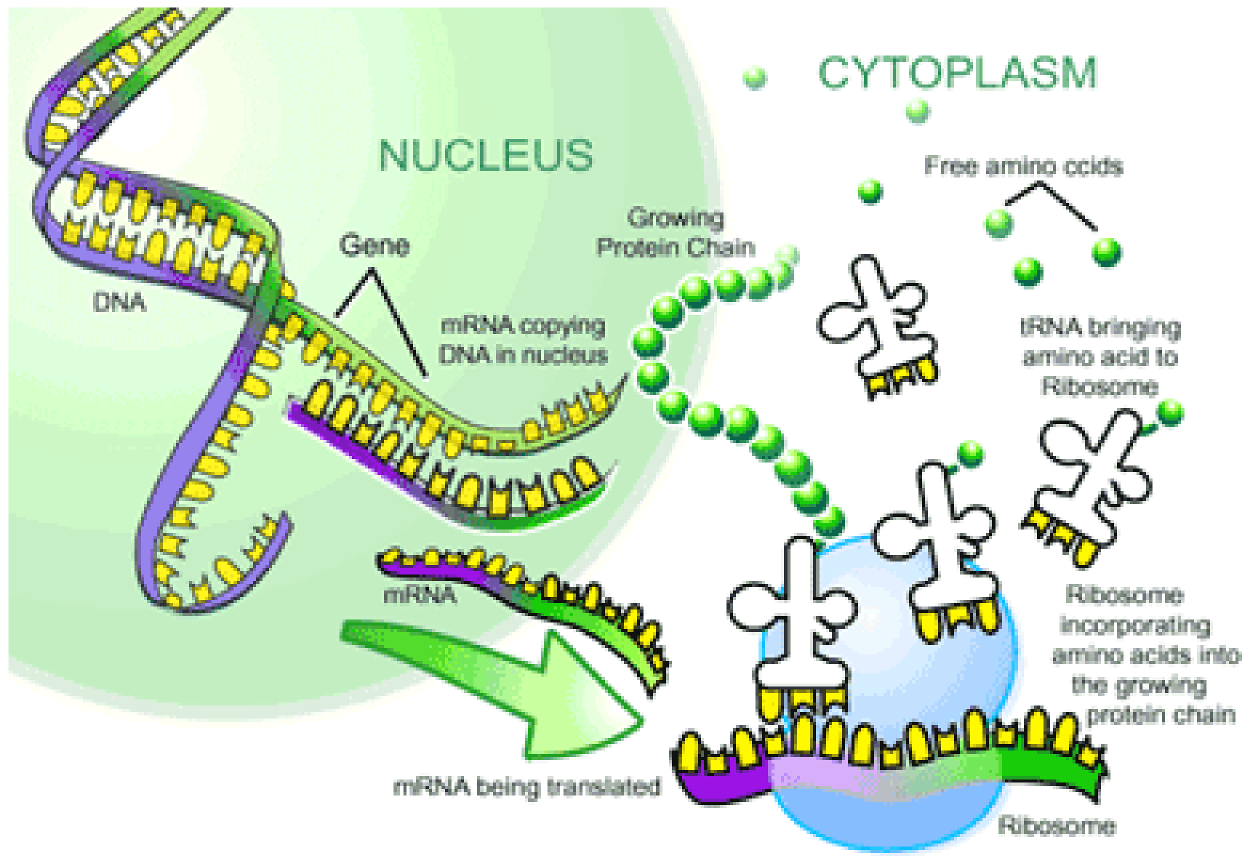
Signaling transcription (in nucleus)

➔ translation (in cytoplasm)

➔ functioning protein

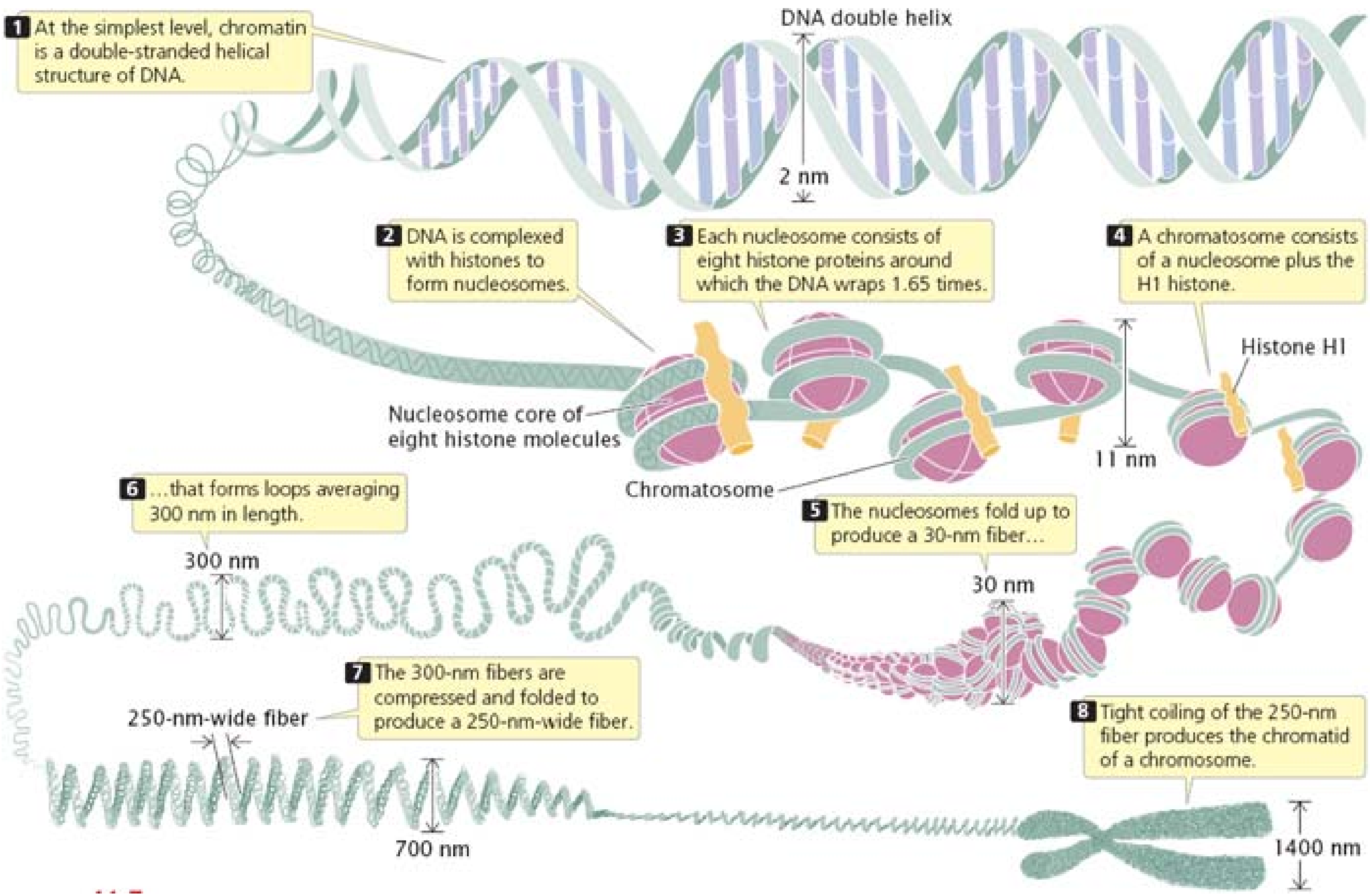
-- extremely complicated!





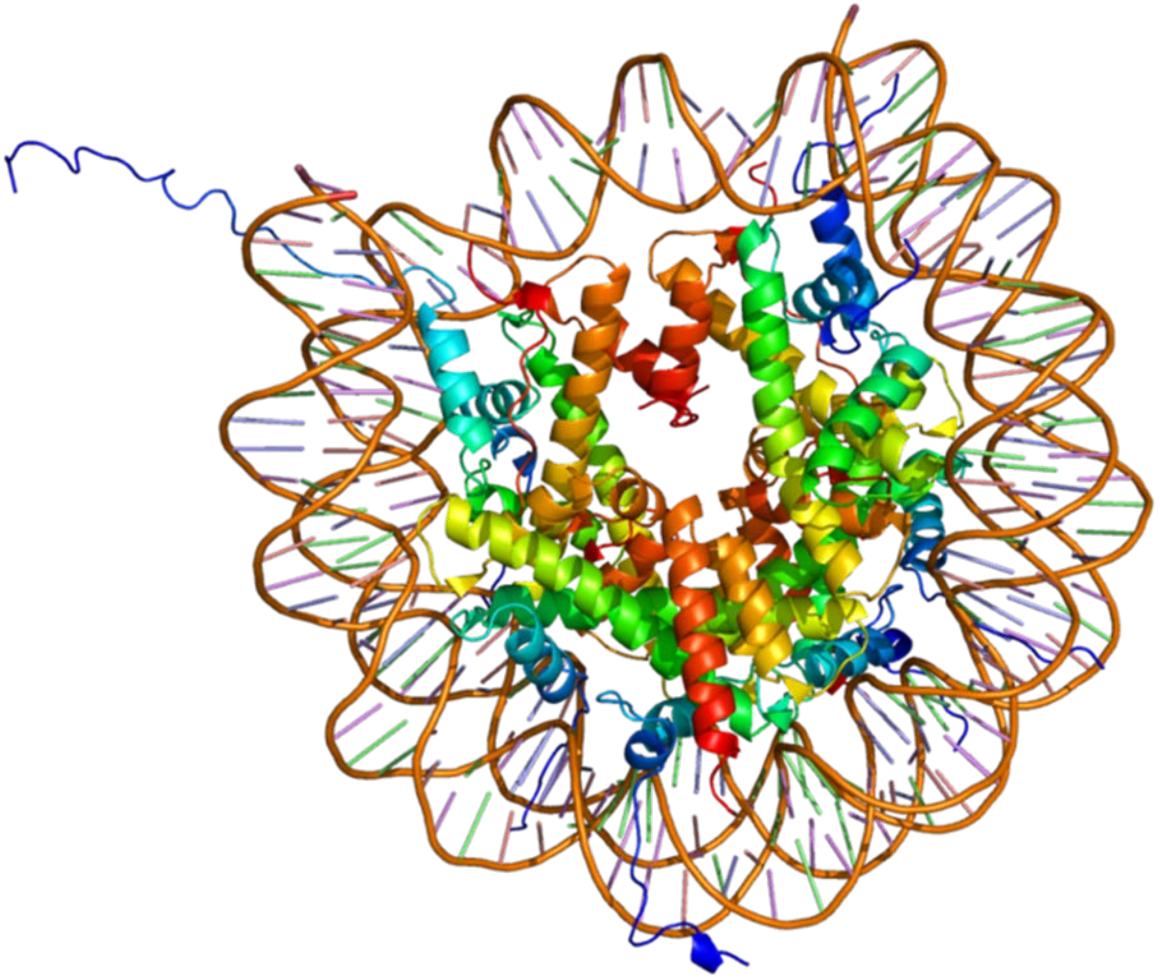
from http://ebbailey.wordpress.com/general-information/dna-to-protein/

The genome is beautifully structured but amazingly complex.



From http://www.nature.com/scitable/topicpage/eukaryotic-genome-complexity-437

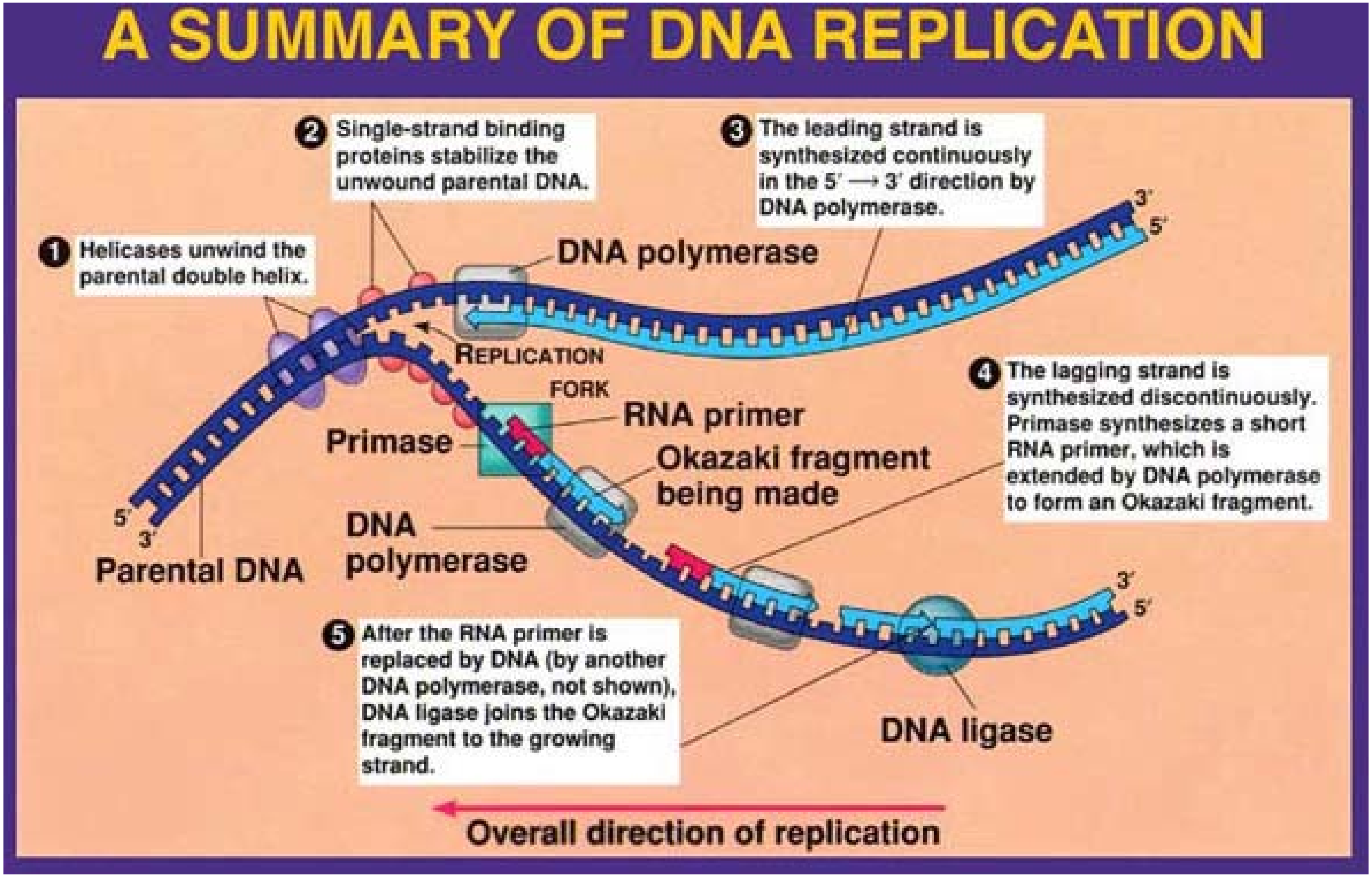
Each protein can be very complicated.



a core histone:
Protein H2AFJ PDB

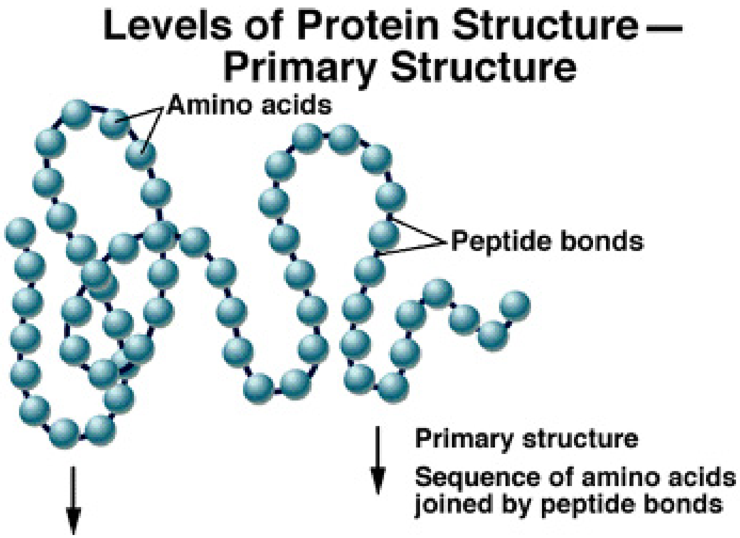
http://en.wikipedia.org/wiki/Histone

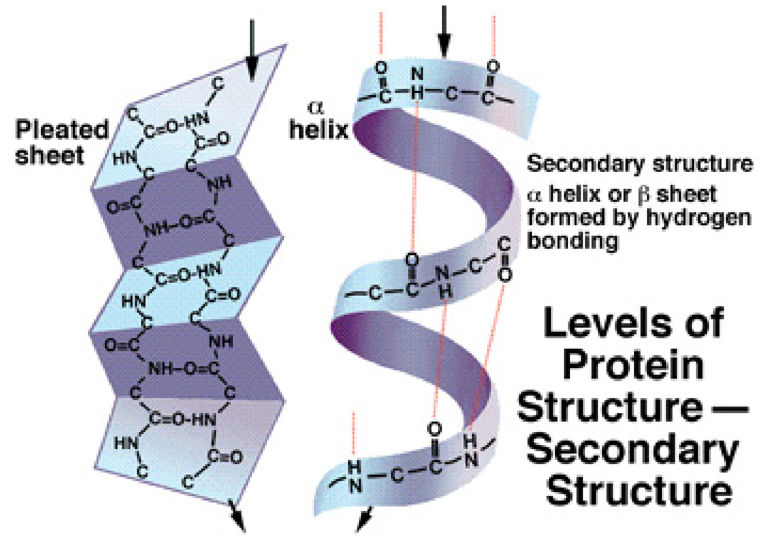
DNA replication is different, but related to DNA ➔ RNA ➔ protein.

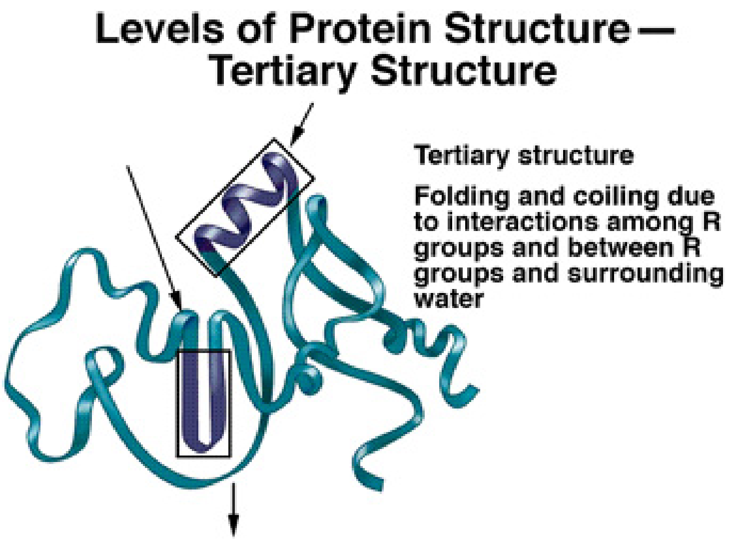


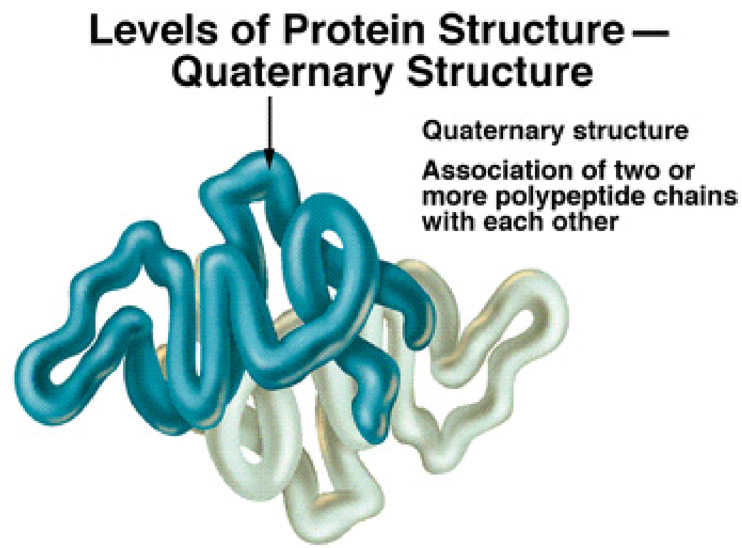
from http://serc.carleton.edu/microbelife/research_methods/genomics/transcrip.html

The proteins have to fold into their native states.









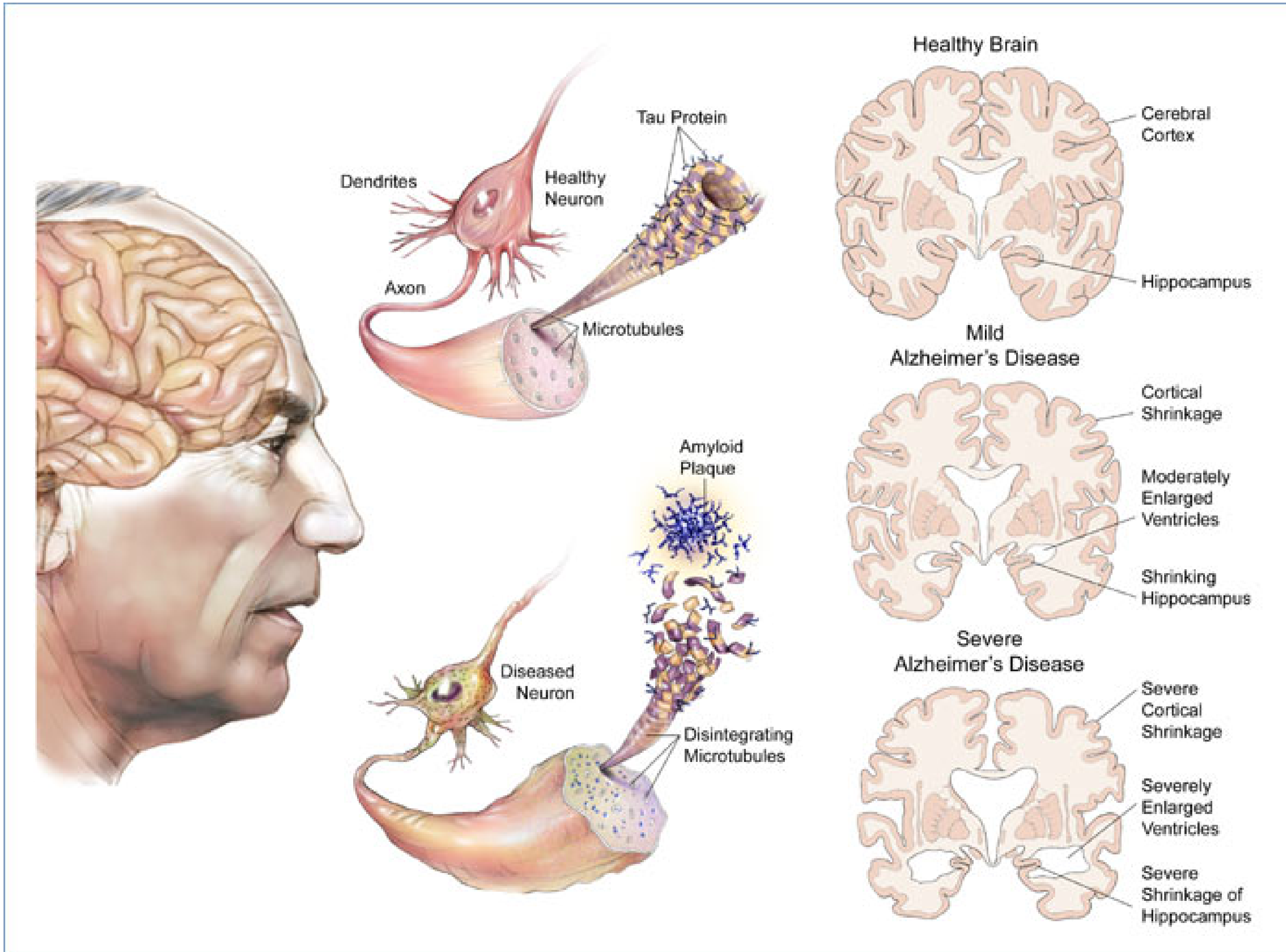
from http://bioserv.fiu.edu/~walterm/

Amyloids, insoluble fibrous protein aggregates, arise from at least 18 inappropriately folded versions of proteins and polypeptides.

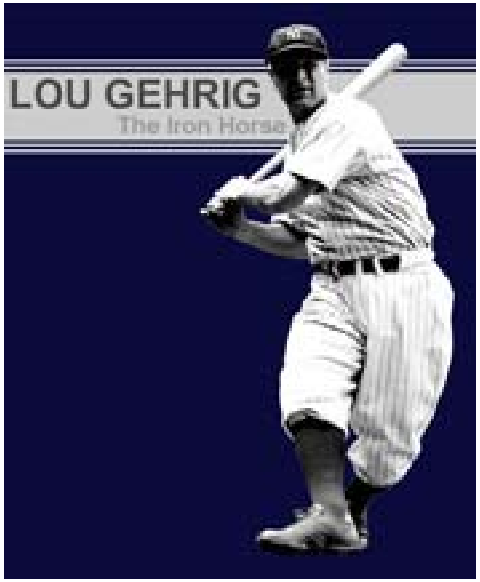
Diseases featuring amyloids:

Alzheimer's disease
Parkinson's disease
Huntington's Disease
Rheumatoid arthritis
Type 2 diabetes
Atherosclerosis
Bovine spongiform encephalopathy
Medullary carcinoma of the thyroid
Cardiac arrhythmias, Isolated atrial amyloidosis
Aortic medial amyloid
Prolactinomas
Familial amyloid polyneuropathy
Several forms of amyloidosis
Lattice corneal dystrophy
Cerebral amyloid angiopathy
Dialysis related amyloidosis
Finnish amyloidosis
systemic AL amyloidosis
Sporadic Inclusion Body Myositis

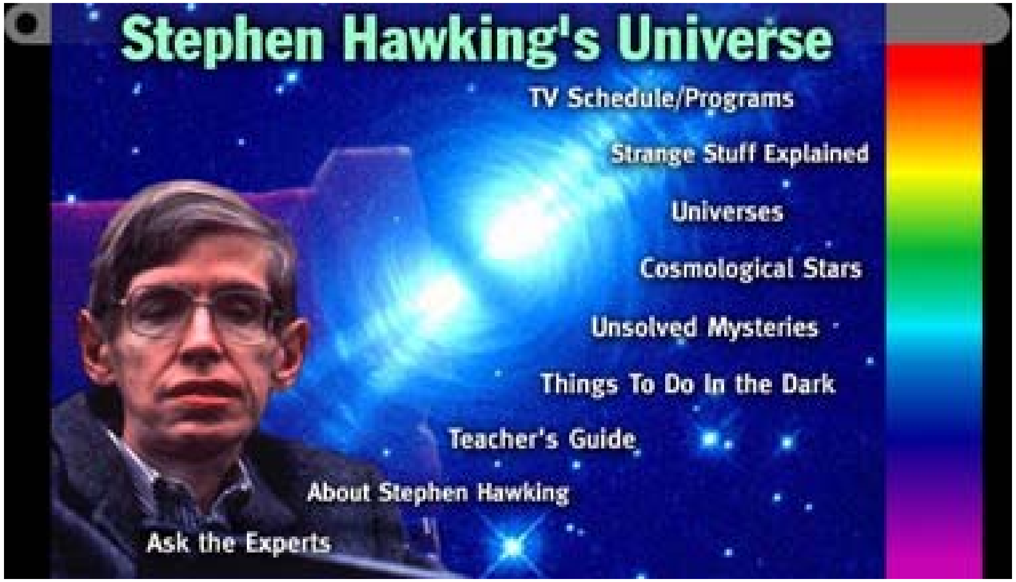
from http://en.wikipedia.org/wiki/Amyloid



from http://sierram.web.unc.edu/



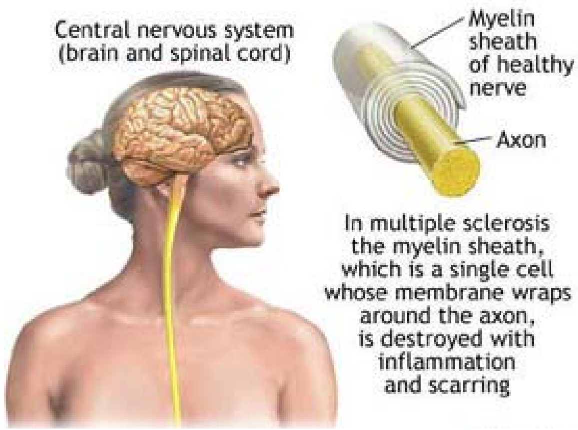
ALS heroes



from http://www.lougehrig.com/

from http://www.pbs.org/

MS heroes



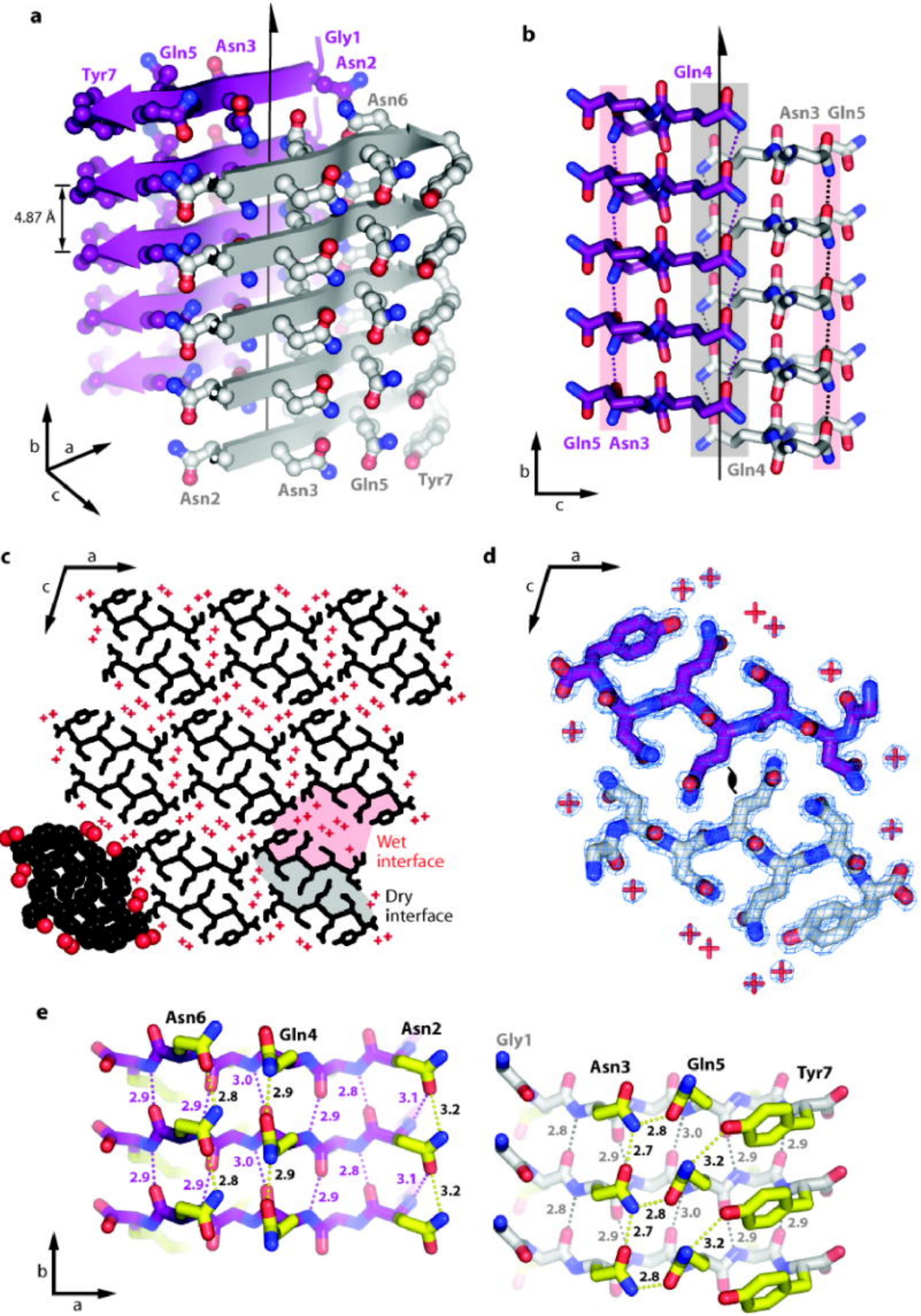
Annette Funicello

http://multiplesclerosis-relief.com/

from www.wellsphere.com

from http://www.thefind.com/gifts/

20



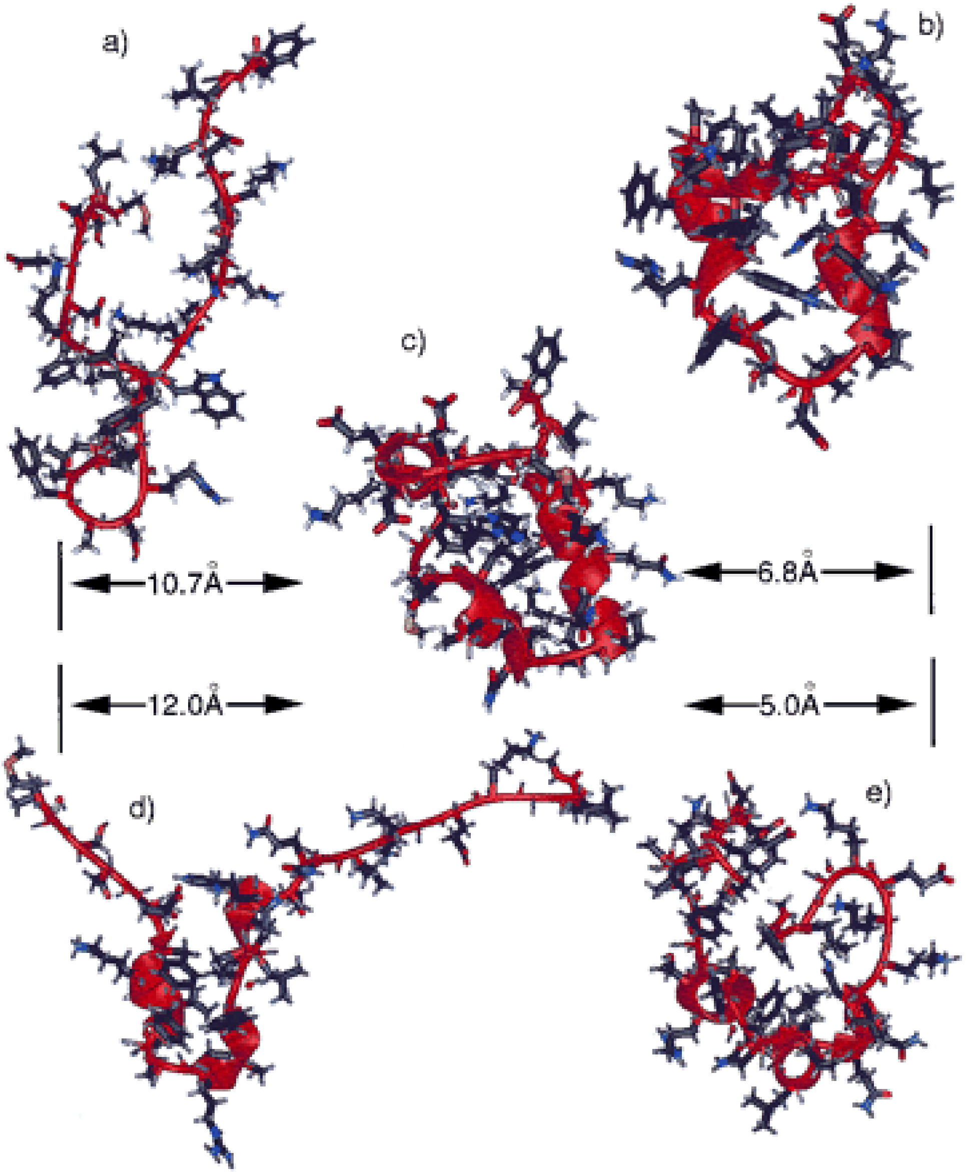
Example of experiment: an X-ray diffraction analysis

Structure of GNNQQNY. Carbon atoms are colored in purple or grey/white, oxygen in red, and nitrogen in blue.

"We selected the yeast protein Sup35 for X-ray diffraction analysis."

"Its fibril-forming tendency had been traced to the N-terminus of the prion-determining domain, and from this region we isolated a 7-residue, fibril-forming segment with sequence GNNQQNY."

From Rebecca Nelson et al., "Structure of the cross-β spine of amyloid-like fibrils", Nature 435, 773 (2005).



Example of theory:
a molecular dynamics simulation

Y. Duan, L. Wang, and P. A. Kollman, "The early stage of folding of villin headpiece subdomain observed in a 200-nanosecond fully solvated molecular dynamics simulation", Proc. Natl. Acad. Sci. 95, 9897–9902 (1998).

Levels of theory:

"microscopic" – e.g., quantum chemistry and molecular dynamics simulations

"mesoscopic" – e.g., modeling of molecular pathways in cell

"macroscopic" – e.g., modeling of processes in whole body

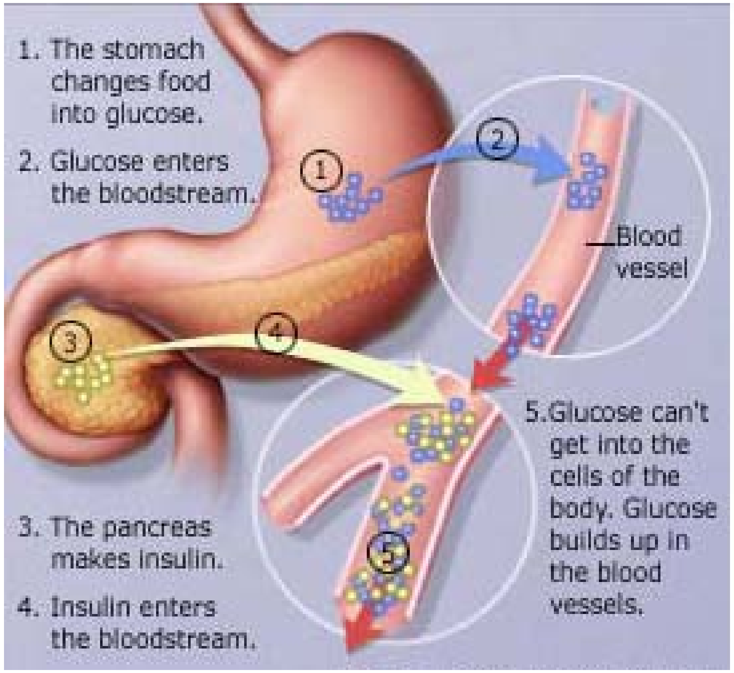
"formal" – e.g., searching for new principles (often without much success)

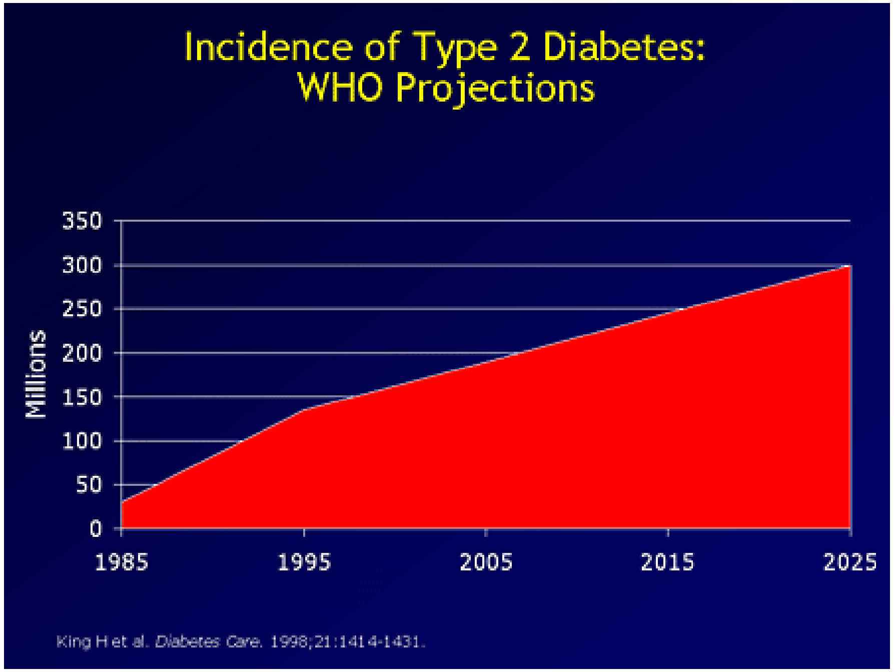
We have developed a general method for calculating the biochemical response to medications or other medical interventions, and applied it in trying to understand a scientific mystery:

Why do people usually show immediate remission of type 2 diabetes when they have bariatric surgery, in which food bypasses most of the stomach and small intestine?

With understanding, perhaps the surgery can be replaced with pharmaceuticals.

We constructed and solved a simple macroscopic model for the effect of bariatric surgery on type 2 diabetes.



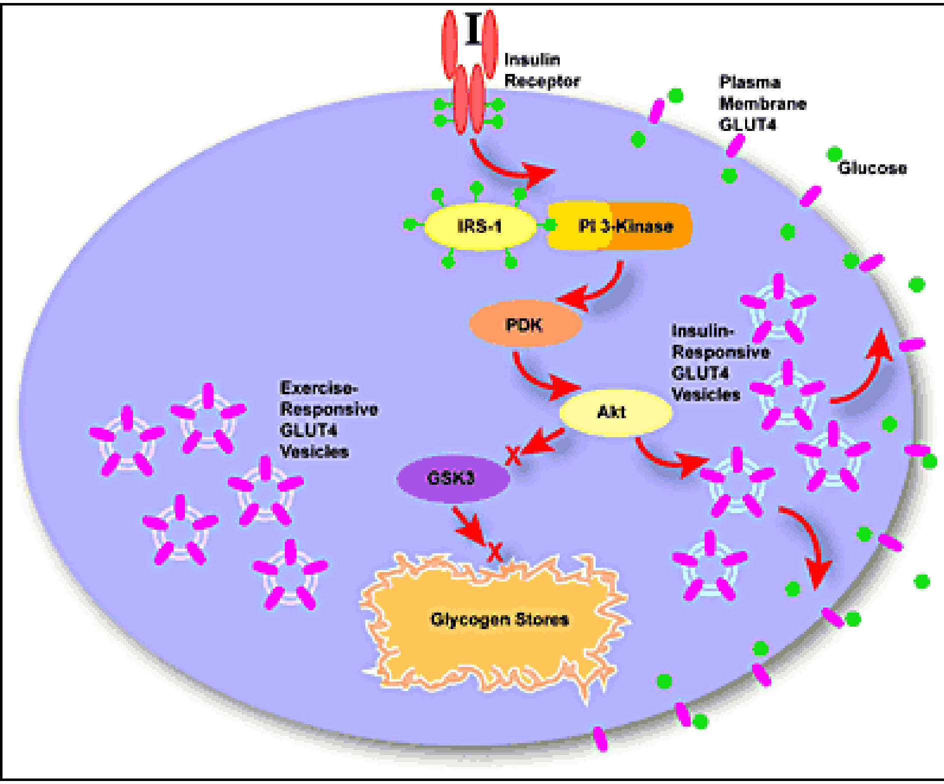


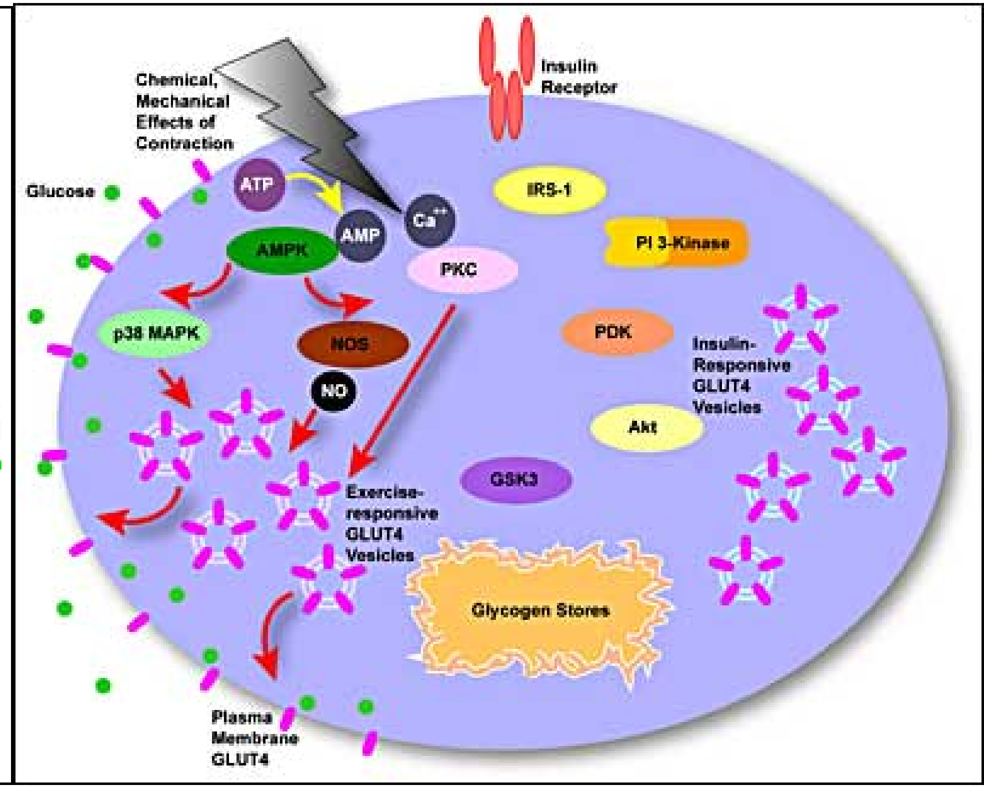
http://www.medicinenet.com/script/main/art.asp?articlekey=42940

http://www.medscape.org/viewarticle/536351

Consequences of type 2 diabetes:

Diabetes is responsible for more than half of lower limb amputations performed in the U.S.
Diabetes is the leading cause of new cases of blindness in adults age 20 – 74.
Risk of heart disease and stroke, nerve damage, vascular injuries, kidney failure.
Increased risk for hearing loss, dementia, respiratory and urinary tract infections, colorectal cancer, uterine cancer, periodontal disease, nonalcoholic fatty liver disease.





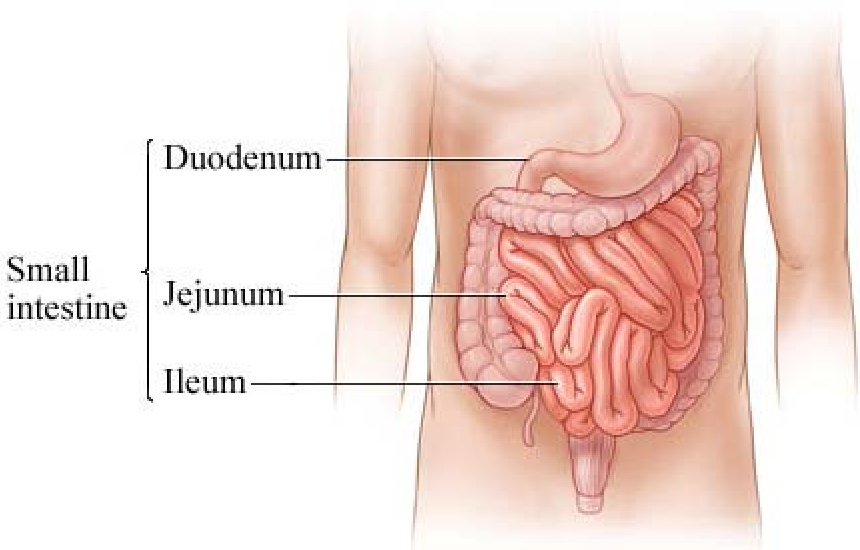
insulin ➔ glucose enters cell

Normal absorption of glucose by muscle and fat cells requires insulin.

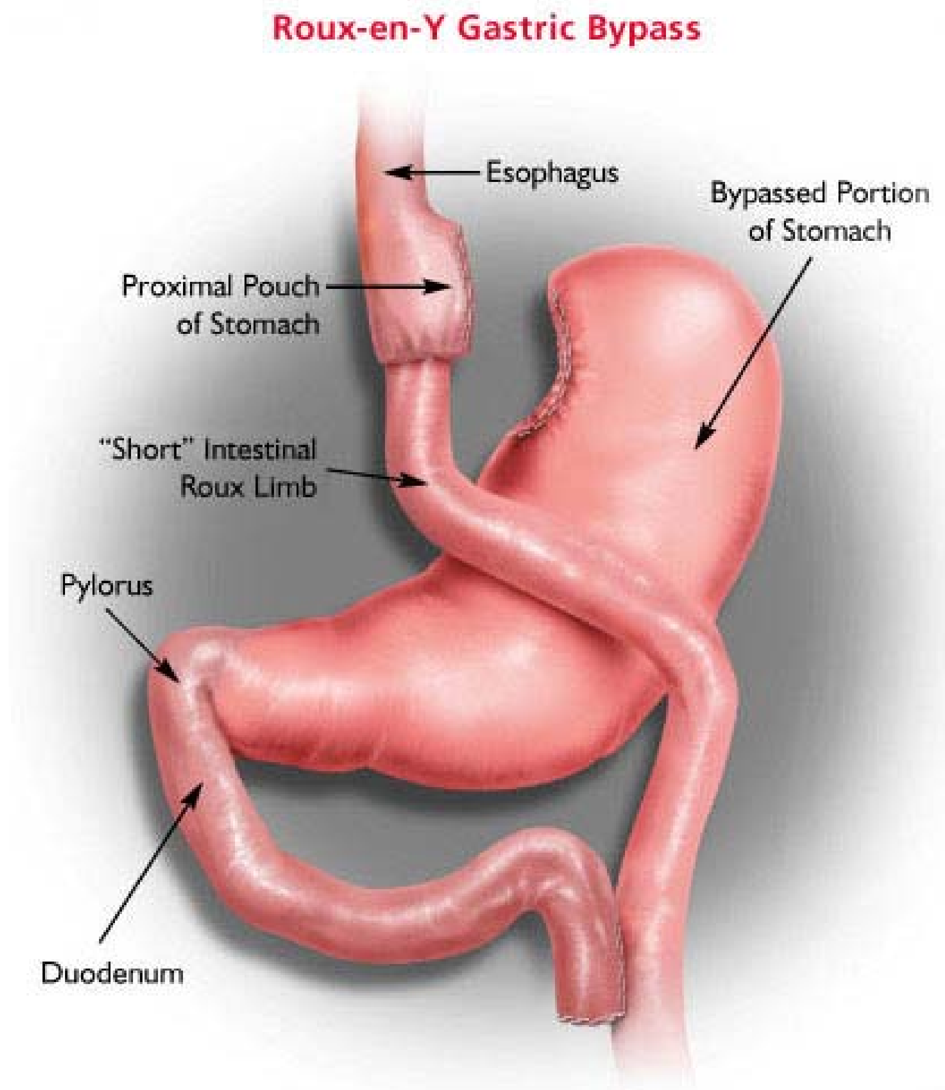
exercise ➔ glucose enters cell

Glucose absorption in muscle cells due to exercise is insulin-independent.

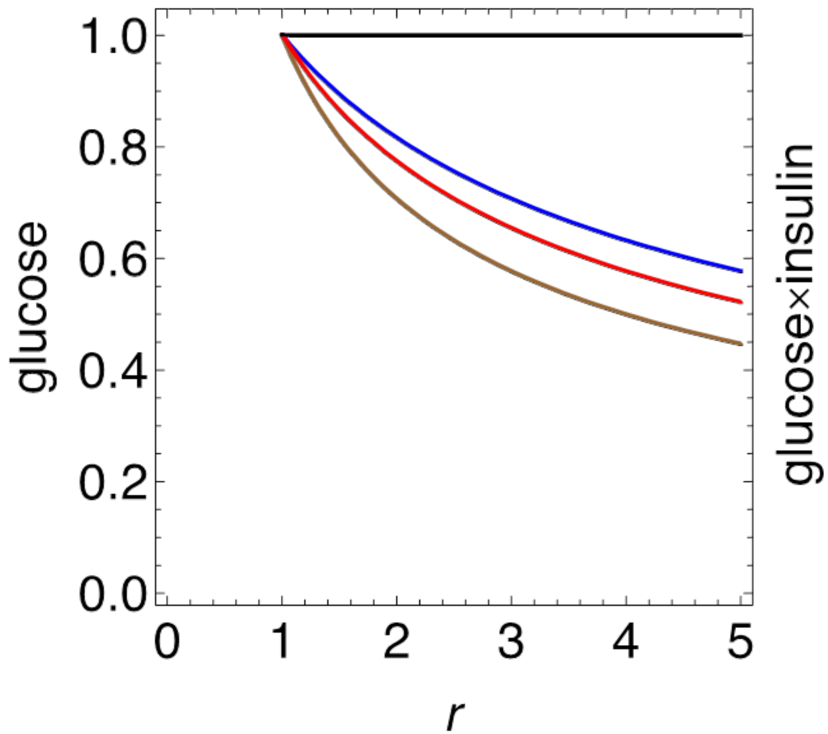
from http://diabetesmanager.pbworks.com/w/page/17680187/Exercise and the Regulation of Blood Glucose



from http://www.webmd.com/



from http://wesley.ehc.com/

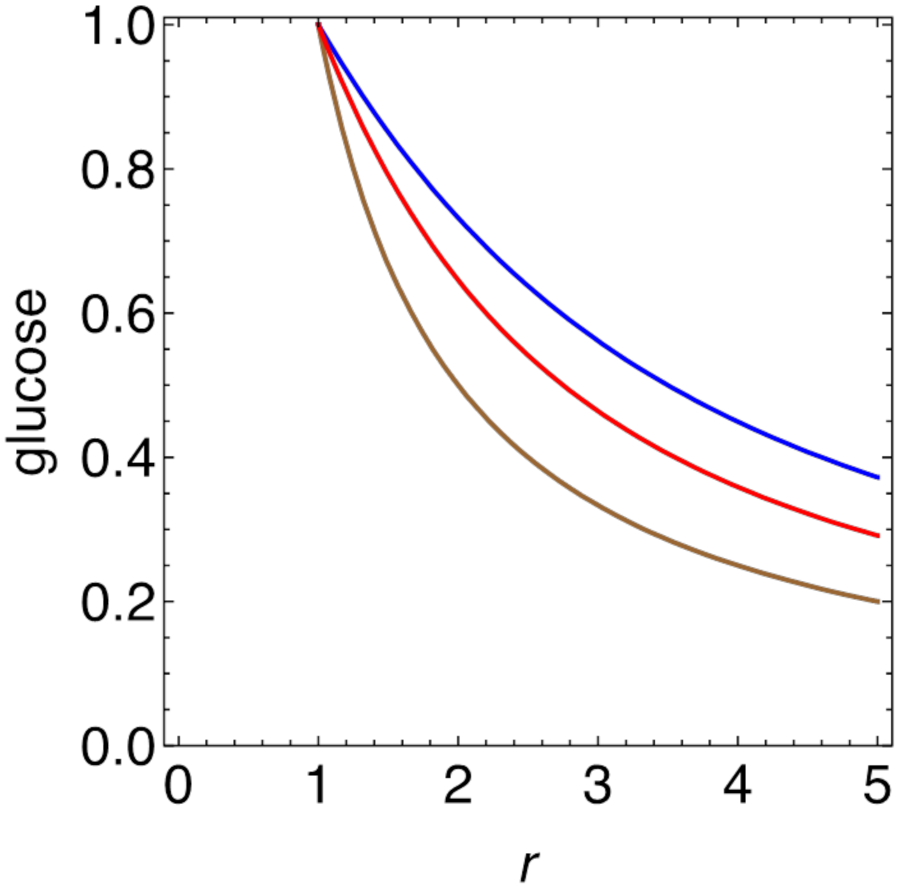


The most popular hypothesis is that bariatric surgery causes an increase in incretins -- biochemicals that combine with glucose to stimulate insulin production.

Then more insulin would cause a faster absorption of glucose by the cells.

This is a 2nd order process, since the glucose must be absorbed twice: by the pancreas to stimulate insulin production, and again by the cells.

Two tests of the hypothesis that an increase in incretin concentration alone can explain the fall in glucose level and insulin resistance immediately after surgery. **The three lower curves show the scaled glucose concentration as a function of the factor *r* by which incretins are increased.** (Observed values of *r* range from 1 to 5, with a clustering below 2.) They correspond to three assumptions regarding the incretin contribution to insulin production: 50% for the top curve, 67% for the middle curve, and 100% for the bottom curve. **Even in the most favorable scenarios, the decrease is insufficient to explain all the observations.** The horizontal line at the top is the scaled insulin resistance = glucose x insulin for all scenarios -- i.e., for all values of *r* and all percentages for the incretin contribution. As found above, it is constant. **In other words, the incretin mechanism alone predicts no decrease whatsoever in insulin resistance. The observations, on the other hand, show a substantial drop in insulin resistance soon after surgery.**



We propose that the bariatric surgery also causes production of some substance which opens an alternative insulin-independent pathway for glucose absorption.

This is a 1st order process, since it is insulin independent.

The drop in glucose level is therefore much larger, and there is now the same drop in insulin resistance, in agreement with the observations.

Glucose concentration as a function of the increase *r* in a substance which opens an alternative insulin-independent pathway for glucose absorption. The top and middle curves are respectively for c_a = 1 and 2, where c_a is the strength of this alternative pathway relative to the normal insulin-dependent pathway in a patient with strong insulin resistance. The bottom curve represents the limit of extreme insulin resistance. **The scaled insulin resistance is given by exactly these same curves, since the insulin level is constant in this case.** If the present mechanism and that of the preceding figure are both operative, there is, of course, an even larger drop in glucose level, and also a substantial drop in insulin resistance .

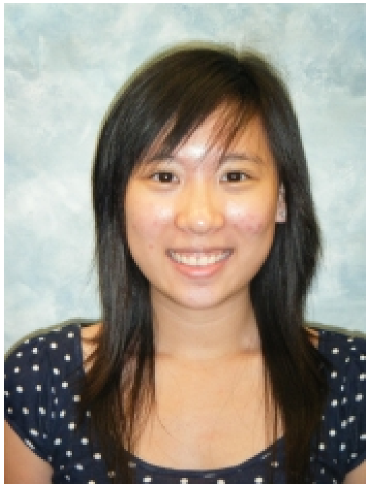
➢ We have addressed the amazing fact that remission of type 2 diabetes is usually achieved immediately after bariatric surgery, long before any appreciable weight loss.

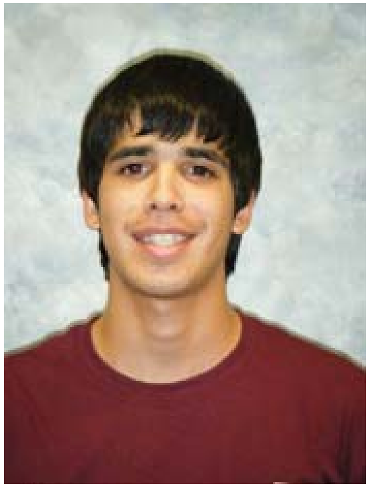
➢This result is ordinarily attributed to a dramatic increase in incretins, but our model indicates that this mechanism alone is not sufficient to explain the largest declines in glucose levels or measured values of insulin resistance.

➢The most robust additional mechanism would be production of a substance which opens an insulin-independent pathway for glucose transport into cells, analogous to the established insulin-independent pathway associated with exercise.

➢If such a substance could be identified, it might be possible to replace the surgery by medication.

These ideas and results were also presented in talks by Jia Ng and Roberto Ortiz at the Fall 2012 meeting of the Texas Section of the American Physical Society.

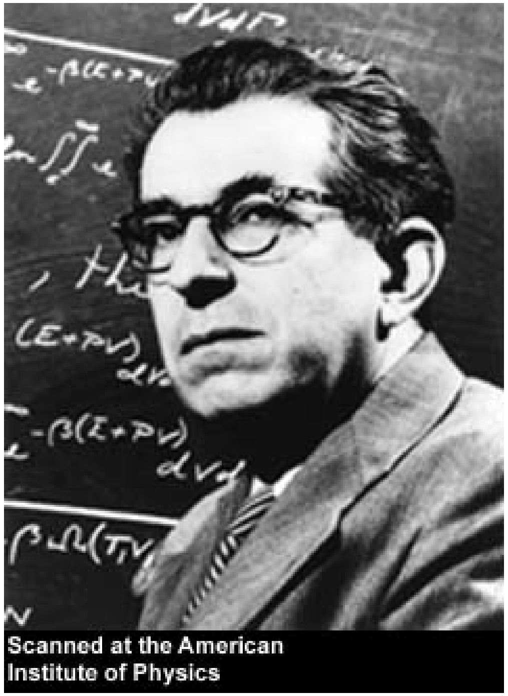

Jia Lerd Ng


Roberto Ortiz

Other collaborators: At Texas A&M, Tyler Hughes; at TAMU Qatar, Michel Abou Ghantous and Othmane Bouhali; at Qatar Biomedical Research Institute, Philippe Froguel and Abdelilah Arredouani.

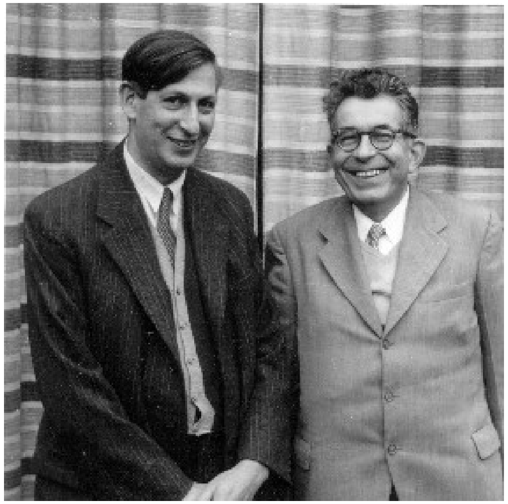
Life in the Higgs condensate, where electrons have mass!

**Note: If the electron had no mass,
there would be no atoms and no us.
So we need the Higgs condensate!**



The Higgs boson, field, and condensate – but should it be called the *London mechanism* for giving mass to fundamental particles, after Fritz and Heinz London?

In 1935, they effectively showed that the photon – the particle of light – has a mass in a superconductor.



**The magnetic field falls to zero in a superconductor
for the same basic reason that the
weak nuclear force has a very short range:
the force-carrying particle has a mass.**

The Higgs condensate is responsible for the masses of both
(1) the W and Z particles which carry the weak nuclear force (responsible for radioactive beta decay) and
(2) fermions like electrons, but in different ways.

W and Z particles $\leftrightarrow$ photon in superconductor, for which

$$\text{mass} \propto \frac{1}{\lambda}\ , \quad \lambda = \text{ penetration depth for magnetic field}$$

fermions like electrons:

mass $\propto$ coupling to Higgs field $\leftrightarrow$ coupling to field of snow

zero or small coupling to Higgs field, as for neutrino: sliding across snow on skis
moderate coupling to Higgs field, as for electron: walking atop snow with snowshoes
large coupling to Higgs field, as for top quark: plodding through snow wearing boots

Higgs field $\leftrightarrow$ field of snow

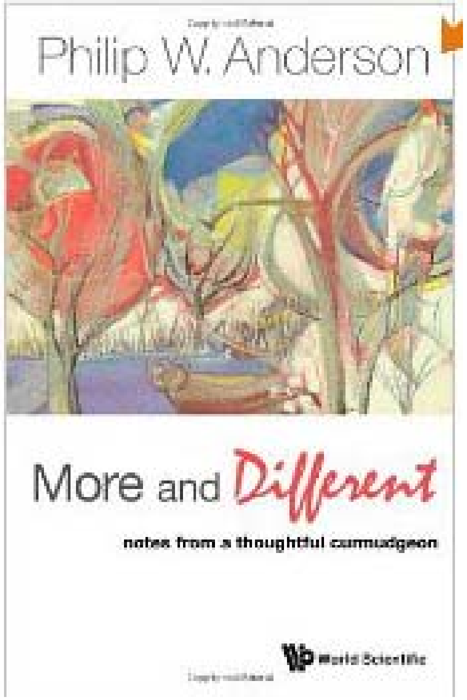
$\Rightarrow$ discovering Higgs boson $\leftrightarrow$ freeing a snowflake

When you walk across a room, you are walking through an incredibly massive condensate.
The mass of your electrons (and quarks) results from this condensate.

However, about 99% of the mass of your *body* results from *E=mc²*, as the quarks and gluons whiz around relativistically inside your protons and neutrons.

Which theorists deserve the Nobel Prize? The Swedish Academy will decide!
We have to use some terminology, and the following seems fair:
London-Anderson-Englert-Brout-Higgs-Guralnik-Hagen-Kibble (LAEBHGHK) *mechanism*
but Higgs *boson*

Phil Anderson (1963) – mechanism
Robert Brout and Francois Englert (August 1964) – mechanism
Peter Higgs (October 1964) – mechanism and boson [with more discussion of boson later]
Gerald Guralnik, Dick Hagen, and Tom Kibble (November 1964) – mechanism

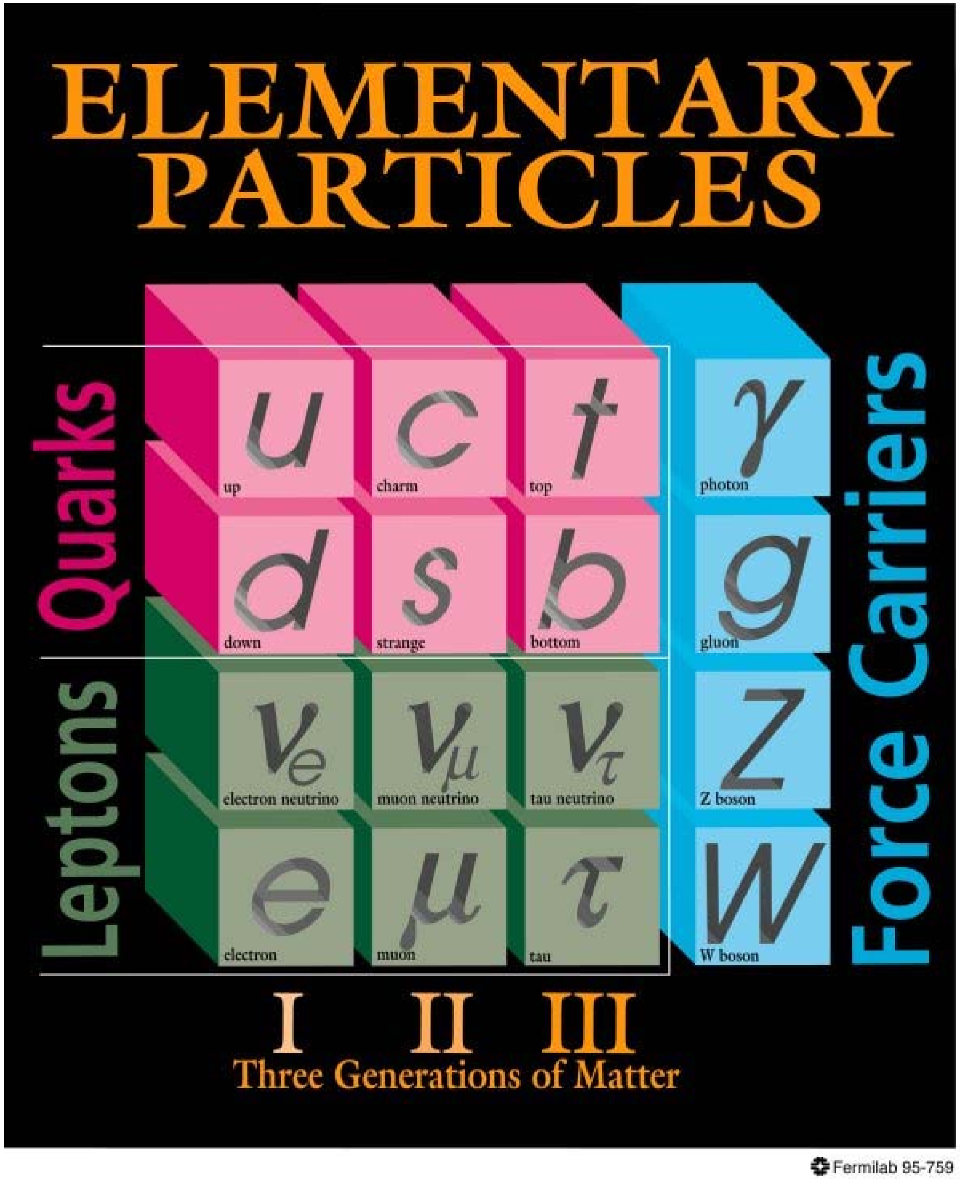



From *More and Different, notes from a thoughtful curmudgeon*:

In 1962 I set out to make my gauge symmetry ideas into a relativistic field theory, and wrote a brief article … which caught the eye of Peter Higgs, who translated it into more acceptable "particlese" and thereby became famous.

To calibrate this statement, you will have to evaluate the modesty of the author, by reading the rest of this fascinating book!

what we now know!



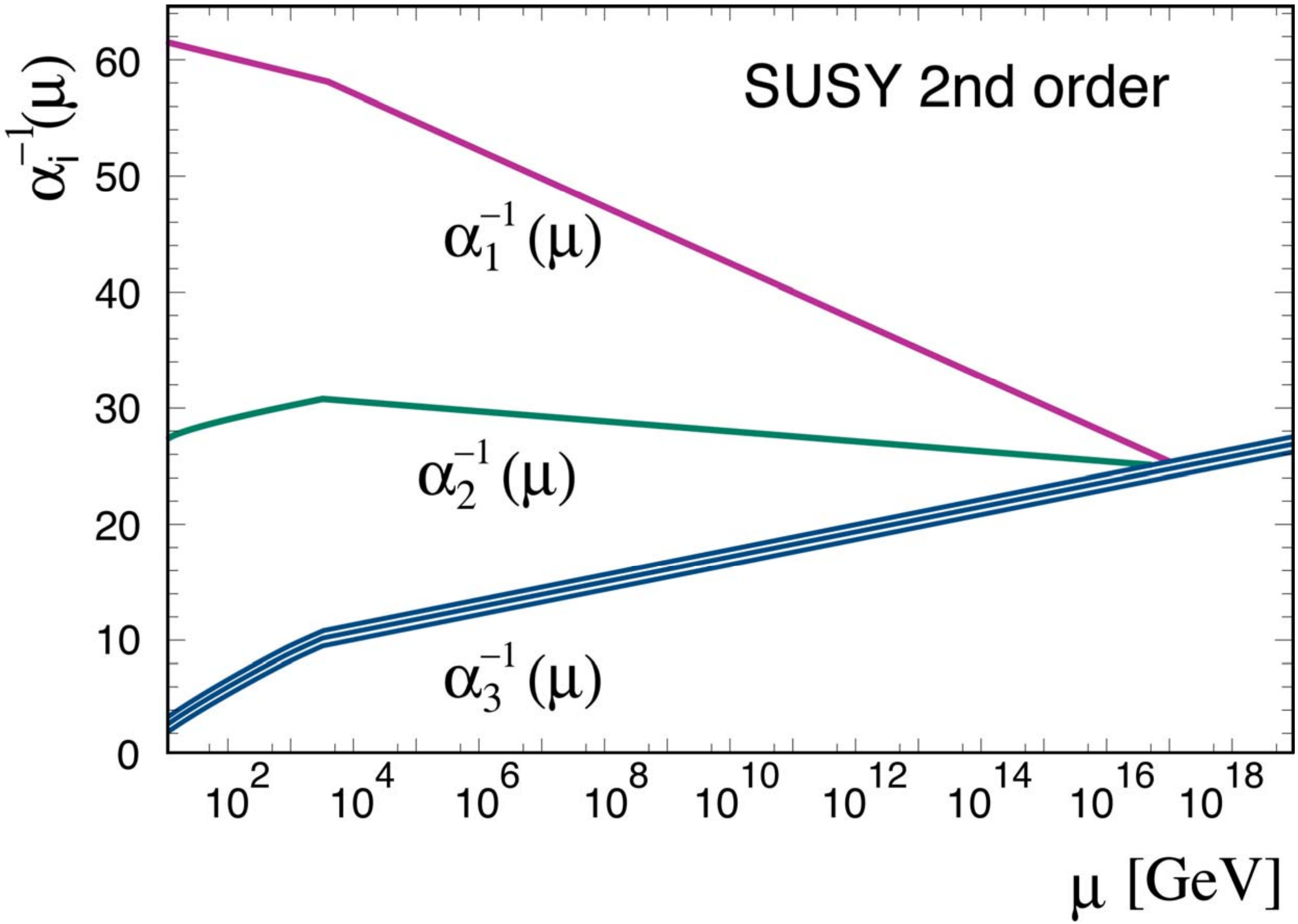
12 spin ½ fermions

4 types of spin 1 bosons

and now the spin 0 Higgs boson

But the Higgs discovery appears to *require* new physics, most likely supersymmetry, for consistency.

Without protection from new physics, virtual processes should drive the mass of the Higgs up to an enormous (ridiculous) energy scale.



Direct evidence for susy: coupling constants of the 3 fundamental forces are unified at the natural energy scale for grand unification.

Without susy, the 3 curves fail to intersect at a common point, so no unification.

Figure from cover of *Relativity, Particle Physics, and Cosmology: Proceedings of the Richard Arnowitt Fest*, edited by R. E. Allen (World Scientific, 1999).

Why do we need grand unification?

Because another rather recent discovery – neutrino masses – appears to require it.

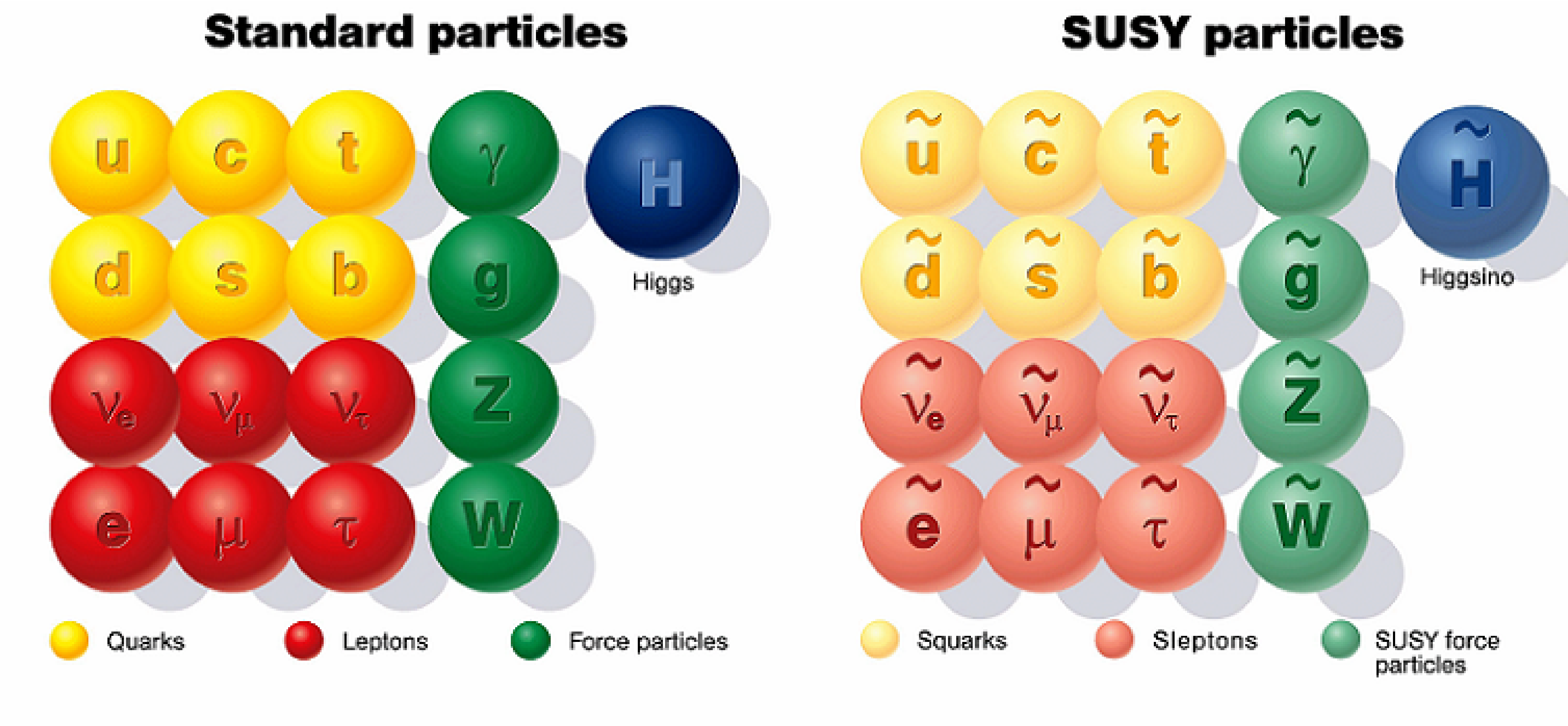
The neutrino mass requires one of two extensions, either of which upsets the delicate requirements for the Standard Model to be mathematically consistent:

For a *Dirac* mass, an extra field has to be added for each generation of fermions.
For *a Majorana* mass, lepton number conservation has to be broken.

But both are natural with grand unification.

So now the electron has a mass.
*A*nd the weak nuclear is very short range because
the force-carrying particles have very large masses.
All this because the Higgs field condensed
as the universe cooled after the Big Bang.

The Higgs seems to point toward supersymmetry.



From http://www.physics.gla.ac.uk/ppt/bsm.htm .

Neutrino masses seem to point toward grand unification of forces, with symmetry-breaking as the universe cooled after the Big Bang.

E.g., $SO(10) \rightarrow SU(5) \times U(1) \rightarrow SU(3)_C \times SU(2)_L \times U(1)_\gamma$.

susy also provides an extremely plausible dark matter candidate, with all the right properties: the (least massive)

neutralino

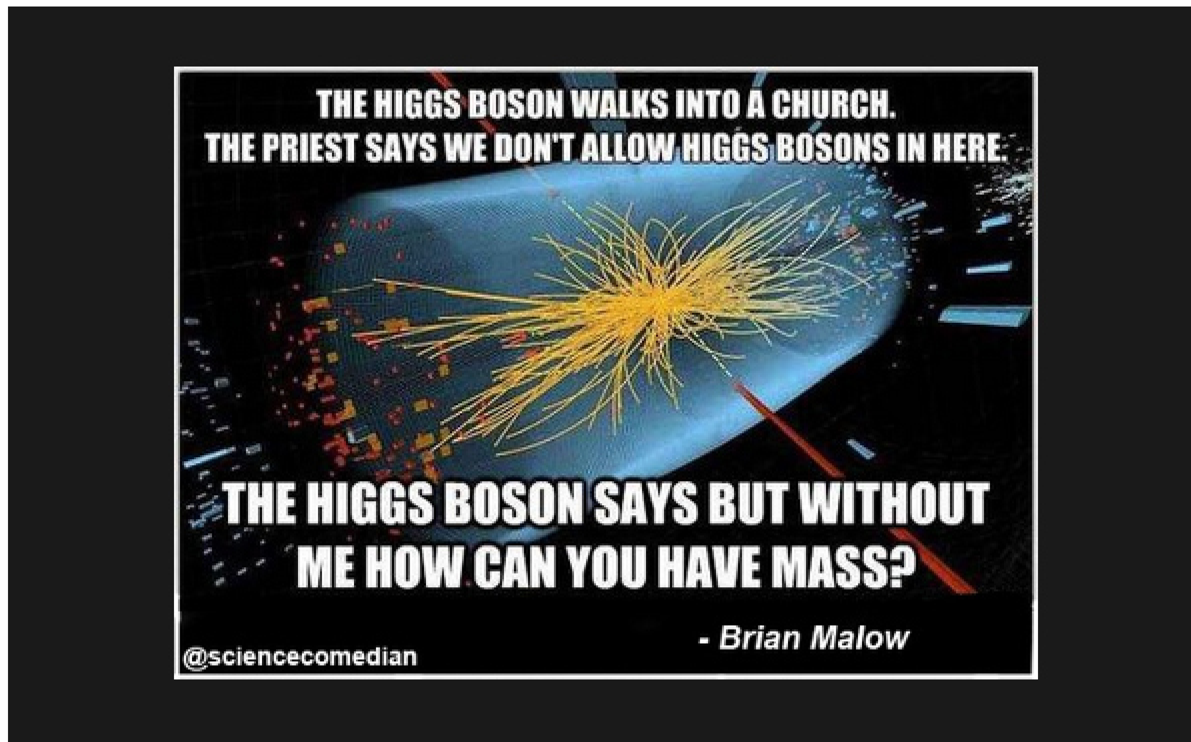
Blue: matter (ordinary and dark) mapped by gravitational lensing

Red: hot gas, representing ordinary matter

The clear separation of dark matter and gas clouds is considered direct evidence that dark matter exists.

From http://apod.nasa.gov/apod/ap060824.html -- NASA Picture of the Day, August 24, 2006

A beautiful theory,
a great experiment,
and a landmark in
human intellectual history,
as the internet clearly reveals.



http://www.buzzfeed.com/cconnelly/28-of-the-best-higgs-boson-jokes-s3x