Historical Overview of the

Periodic Paralyses

By Patrick E. Cochran, and the Judy Tuttle Memorial Research Library

A Rare Value

To emphasize the value of studying human variants, Sir Archibald Garrod (1909), quoted a letter written by William Harvey in 1657:

Nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows traces of her workings apart from the beaten path; nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the usual law of Nature by careful investigation of cases of rarer forms of disease. For it has been found, in almost all things, that what they contain of use or application is hardly perceived unless we are deprived of them, or they become deranged in some way.

(Scriver, Beaudet, Sly, and Valle, 1995).

Reviewing the Literature

Dr. Thera P. Links (1992), has provided a detailed account of her work with a large family in The Netherlands representing some 120 individuals from five generations suffering from Familial Hypokalemic Periodic Paralysis. As briefly outlined by Dr. Links, a number of hypotheses were suggested during the latter part of the 19th century to explain the paralytic attacks in the periodic paralyses.

Links suggests that the early descriptions (those of Talbott),

"seem rather atypical, so that a correct interpretation of the clinical features is not possible."

First Mention

- **Adams, Victor, and Roper (1997), list Hartwig, as providing the first unmistakable account of Hypokalemic Periodic Paralysis in 1874.**
- **Also according to Adams, Victor, and Ropper (1995), the first of the myotonic disorders to be recognized was *myotonia congenita*.**

Stepping Stones

- **Julius Thomsen, a Danish physician described the autosomal dominant form of *Myotonia Congenita* in 1872. Thomsen's designation, though inaccurate, was *ataxia muscularis.***
- **Strumpell, in 1881, assigned the name *myotonia congenita.***
- **Westphal, in 1883, referred to this same disorder as *Thomsen's disease*.**

Early Characterization

- **In 1885, Westphal suggested that the cause of periodic paralysis could be found "in the muscle itself."**
- **Oppenheim (1891), also provided early discussion of this disorder.**
- **Goldflam (1895), provided important descriptions of "vacuoles in muscle biopsy tissue samples."**

Early Characterization

- **Kuttner (1929) was the "first to observe potassium depression" in the blood during paralytic attacks of Hypokalemic Periodic Paralysis.**
- **Biemond and Polak Daniels (1934), were "the first to suggest that it was a chemical alteration in the muscles" that brought on the attacks in HypoKPP.**

Early Characterization

- **Aitken (1937), confirmed the "importance of Hypokalemia" in the periodic paralysis attacks.**
- **Talbott (1941), summarized all 400 cases of periodic paralysis that had been reported prior to 1941, but in most cases no information was obtained about the serum potassium**

Early Characterization

- **In 1951, Tyler and colleagues "first described Primary Hyperkalemic Periodic Paralysis," distinguishing it from the more common Hypokalemic form.**

- **Gamstorp described two additional families in 1956, and named it *adynamia episodica hereditaria*.**

Building on the Record

- **Two decades later, Buruma (1978, and 1979), provided an extensive historical survey of HypoKalemic Periodic Paralysis.**

- **Thera P. Links published her comprehensive thesis on Familial Hypokalemic Periodic Paralysis in 1992.**

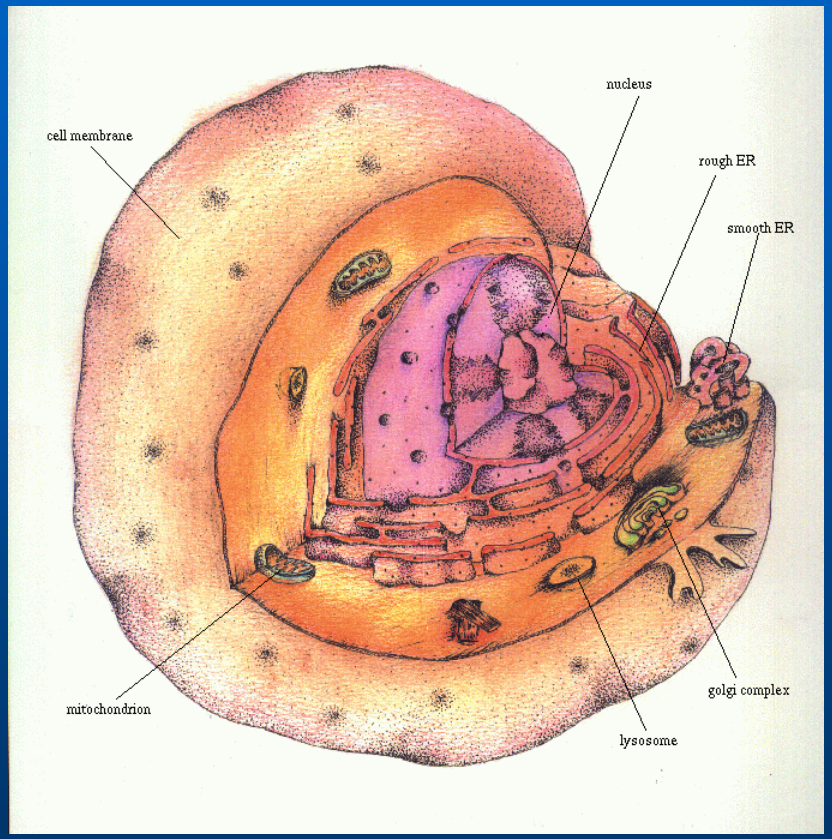
The Journey Continues

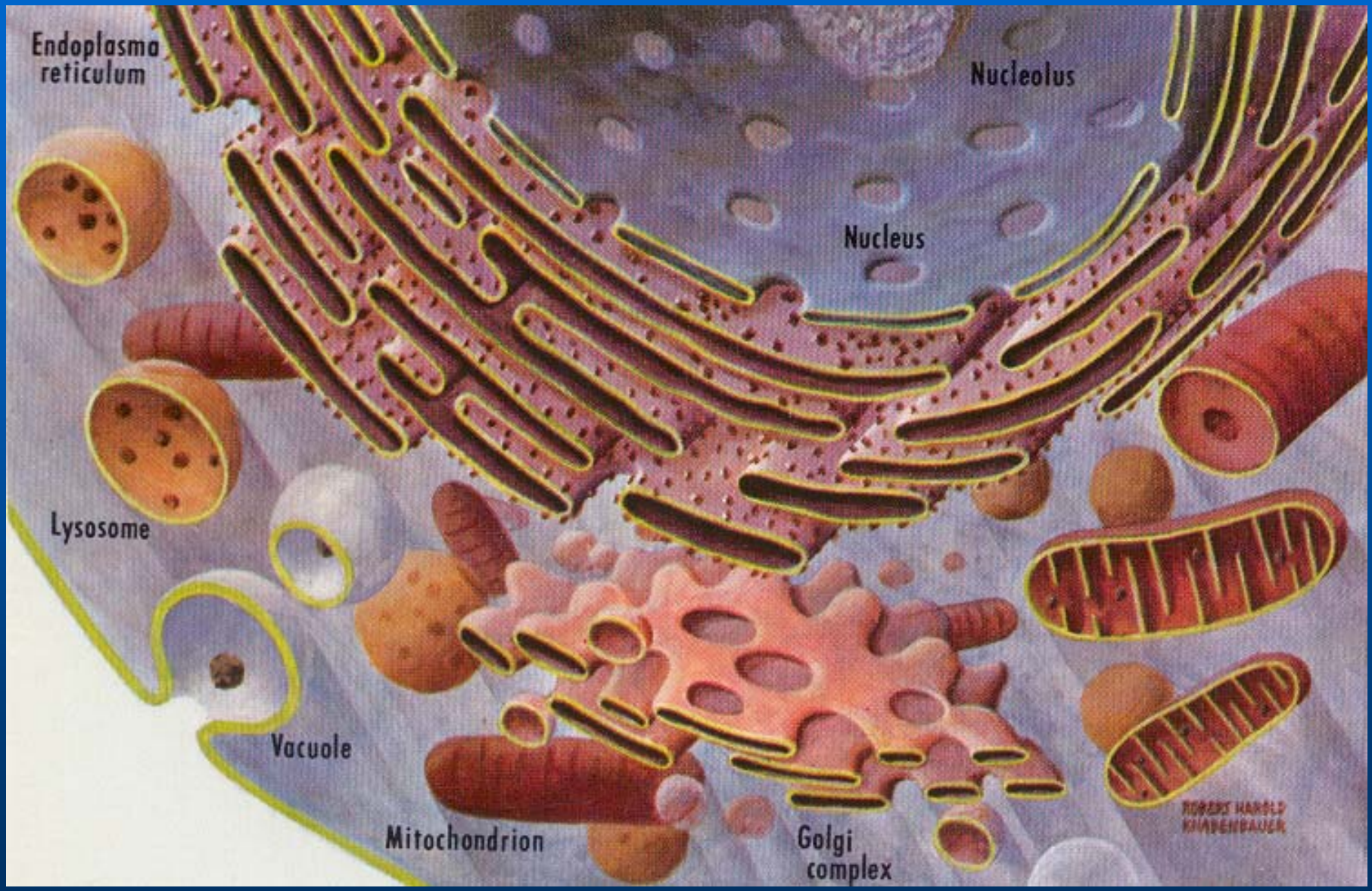
- **Several forms of hereditary periodic paralysis have been linked to mutations of the skeletal muscle Sodium channel, to Calcium channels, to Chloride channels, and Dr. Links and others have thought that variants will be linked to Potassium channels. . .**

Revolutionary Thinking

According to Petty (1993), the modern study of **biological membranes** began in 1925 by Fricke and, independently, by Gorter and Grendel.

By the mid-1950s the new world of the cell could be seen with **electron microscopes**. Until the middle to late 1960s, however, membranes were considered to be **static wax-like** structures, similar to bricks in a wall. The first evidence suggesting differently came from **magnetic resonance imagery (MRI)**.




Endoplasma reticulum
Nucleolus
Nucleus
Lysosome
Vacuole
Mitochondrion
Golgi complex

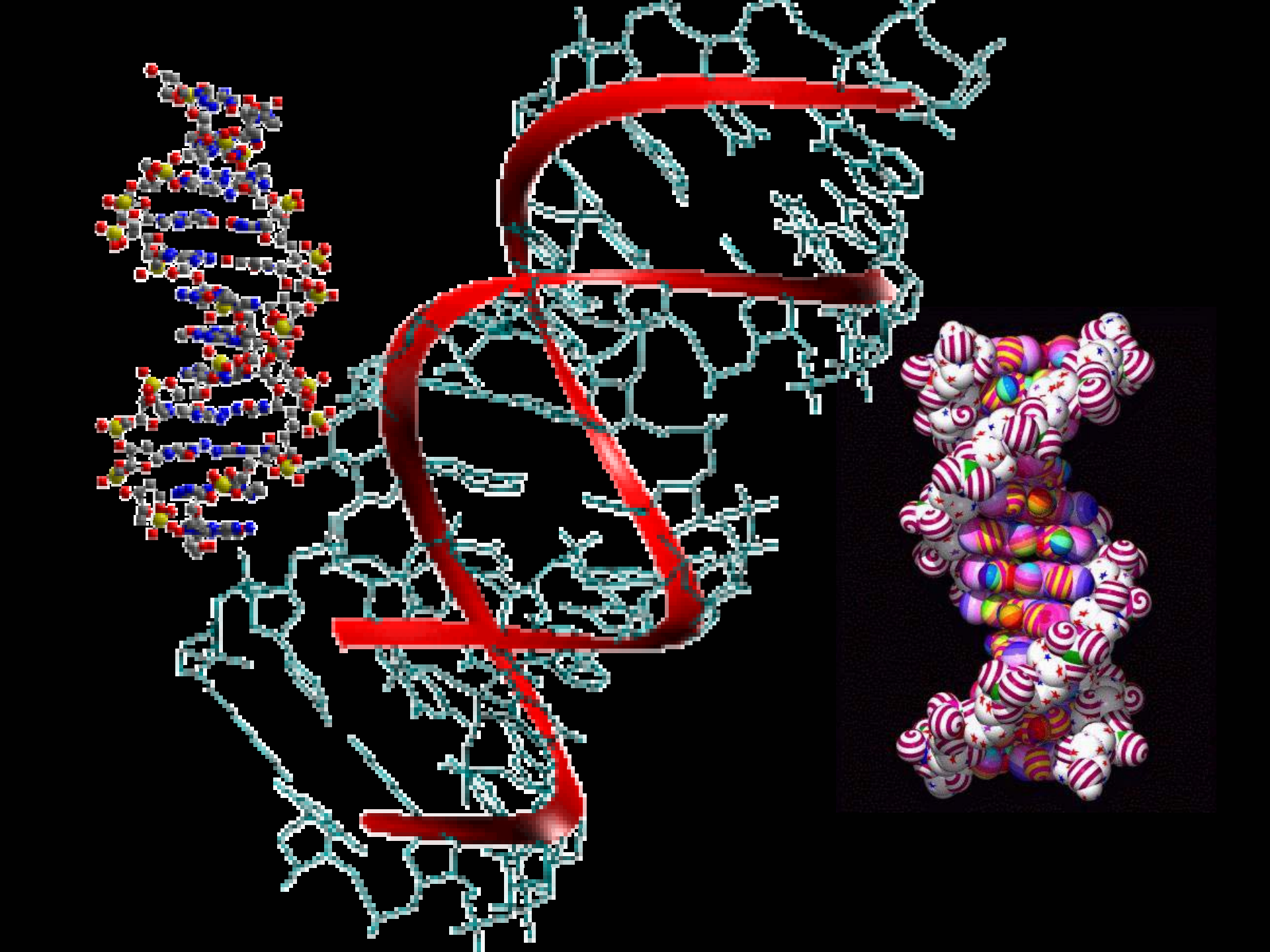
A New Paradigm

1953

J. Dwight D. Eisenhower became our

Thirty-Fourth President 1953-1961

J. D. Watson and F. H. C. Crick propose a model For the DNA molecule comprised of two helically intertwined chains tied together by hydrogen bonds between the purines and pyrimidines.



BLAZING A GENETIC TRAIL

A BRIEF KEY TO BASIC GENETICS

A human cell.
Each of the 100 trillion cells in the human body (except red blood cells) contains the entire human genome—all the genetic information necessary to build a human being. This information is encoded in 6 billion base pairs, subunits of DNA. (Egg and sperm cells each have half this amount of DNA.)

The cell nucleus.
Inside the cell nucleus, 6 feet of DNA are packaged into 23 pairs of chromosomes (one chromosome in each pair coming from each parent).

A chromosome.
Each of the 46 human chromosomes contains the DNA for hundreds or thousands of individual genes, the units of heredity.

A gene.
Each gene is a segment of double-stranded DNA that holds the recipe for making a specific molecule, usually a protein. These recipes are spelled out in varying sequences of the four chemical bases in DNA: adenine (A), thymine (T), guanine (G), and cytosine (C). The bases form interlocking pairs that can fit together in only one way: A pairs with T; G pairs with C.

A protein.
Proteins, which are made up of amino acids, are the body's workhorses—essential components of all organs and chemical activities. Their function depends on their shapes, which are determined by the 50,000 to 100,000 genes in the cell nucleus.

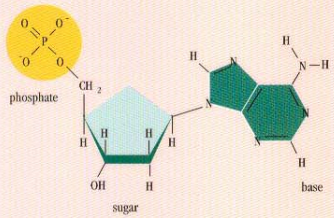
TABLE OF CONTENTS
HHMI HOMEPAGE

Genes, DNA & Nucleic Acid

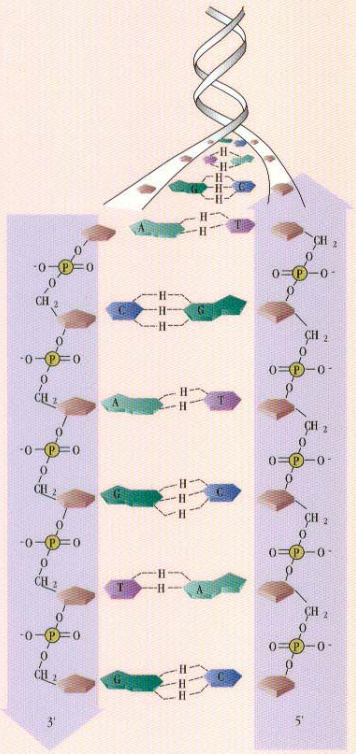
A. Gene functions:
1. To be preserved and transmitted.
2. To control various biological functions through the production of proteins (i.e., large, complex sequences of amino acids) and RNA.

B. Gene structure - two types of nucleic acids:
1. Deoxyribonucleic acid (DNA)
2. Ribonucleic acid (RNA)

C. Nucleotides: the components of nucleic acids - three subunits:



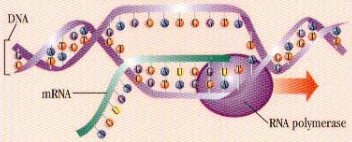
1. Sugar (deoxyribose in DNA; ribose in RNA)
2. Phosphate
3. Nitrogenous base (5 possible bases)
   a. In DNA, the nucleic acid of chromosomes, four nitrogenous bases are found: adenine (A), guanine (G), cytosine (C), and thymine (T).
   b. RNA consists of similar bases, except uracil (U) replaces thymine (T).
   c. DNA is a double helix molecule: (similar to a spiral staircase or twisted ladder), with the sides formed by repeating sugar-phosphate groups from each nucleotide, and the horizontal portions (i.e., steps) formed by hydrogen bonds involving A with T or C with G.
   d. Hereditary information: (i.e., genes) found along the linear sequence of nucleotides in the DNA molecule.



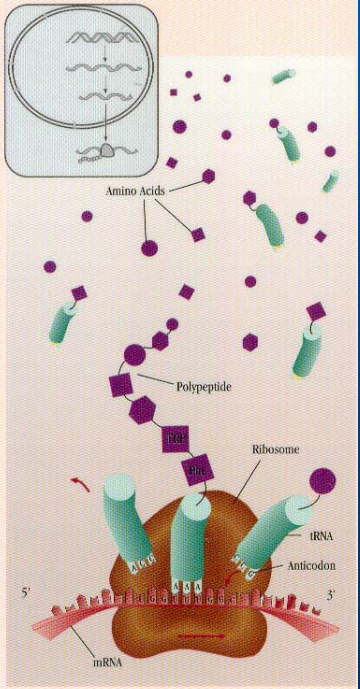
The Central Dogma

A. Replication:
1. DNA is copied from other DNA, by unzipping the helix and pairing new nucleotides with the proper bases (i.e., A with T and C with G) on each separated side of the original DNA.

B. Transcription:
1. Messenger (m)RNA is copied from DNA, by unzipping a portion of the DNA helix that corresponds to a gene.
2. Only one side of the DNA will be transcribed, and nucleotides with the proper bases (A with U and C with G) will be sequenced to build pre-mRNA.
3. Sequences of nucleotides called introns are removed and the remaining segments called exons are spliced together.
4. the mature mRNA leaves the nucleus to be transcribed by the ribosomes.

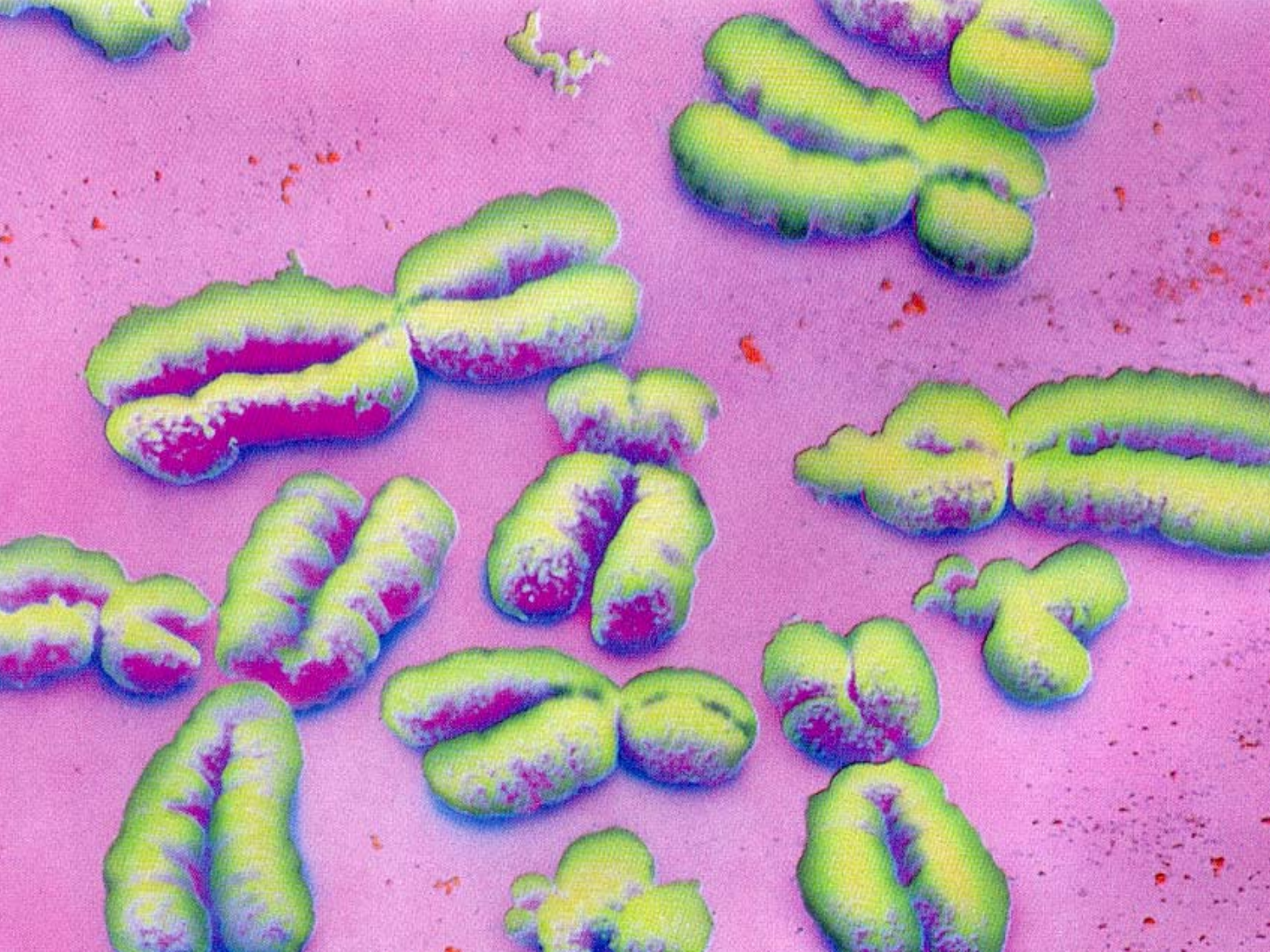


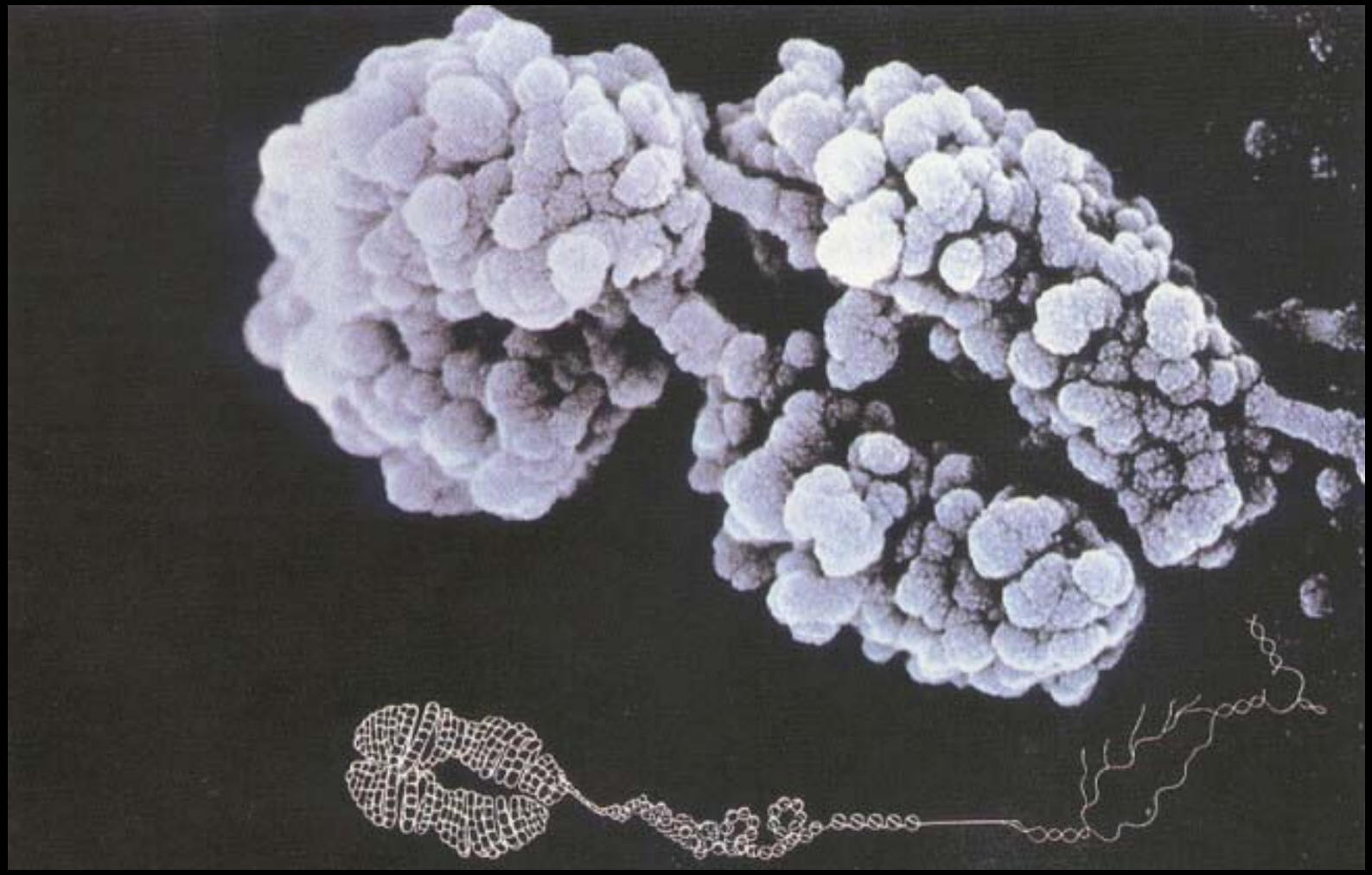
C. Translation:
1. Proteins are synthesized from (m)RNA by ribosomes (which are composed of ribosomal (r)RNA and proteins) which read from a triplet code (i.e., codons) that is universal.
2. The ribosomes instruct transfer (t)RNA's to bring in specific amino acids in the sequence dictated by the mRNA, which in turn was built based on the sequence of nucleotides in the original gene portion of the DNA.



Mutations

Any random, permanent change in the DNA molecule. Many are harmful, some have no effect, and a few actually benefit the organism. Nature selects those mutations that are beneficial or adaptive in organisms to help shape the course of evolution.



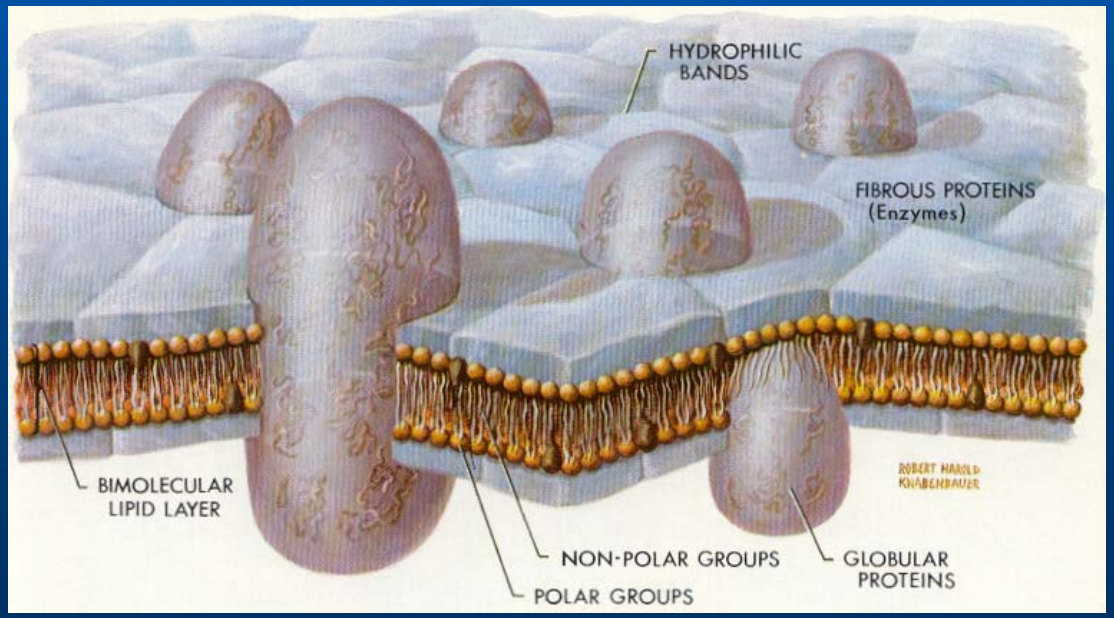


Channeling

In 1953, Alan Hodgkin and Andrew Huxley, Investigated the potassium permeability of nerve axons. They were the first to use the word "channel," to describe their ideas.

A Sea of Activity. . . .

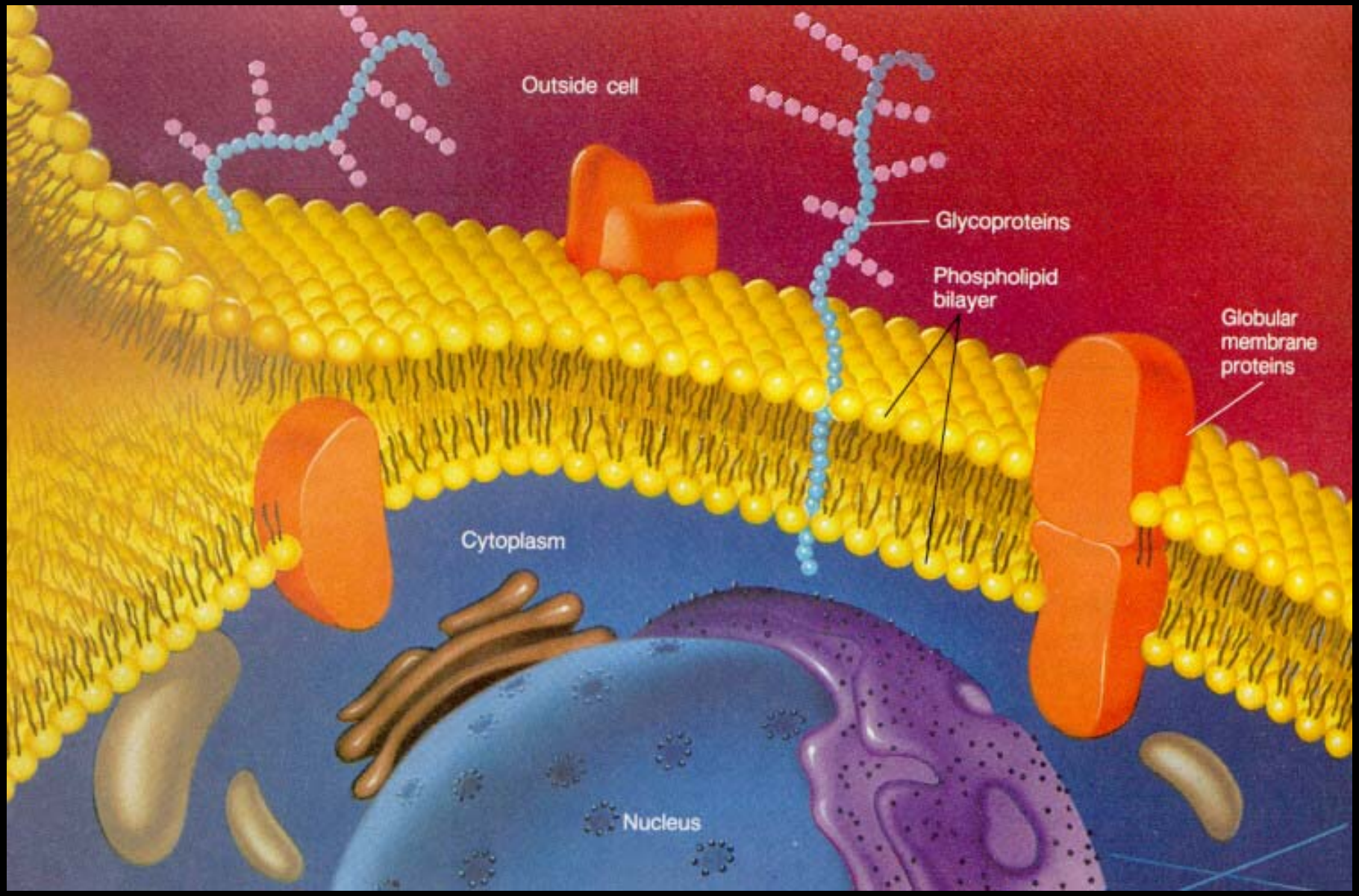
In 1970, Frey and Edidin discovered that membrane proteins possess a lateral mobility, emphasizing the dynamic, or fluid state of cell membranes.



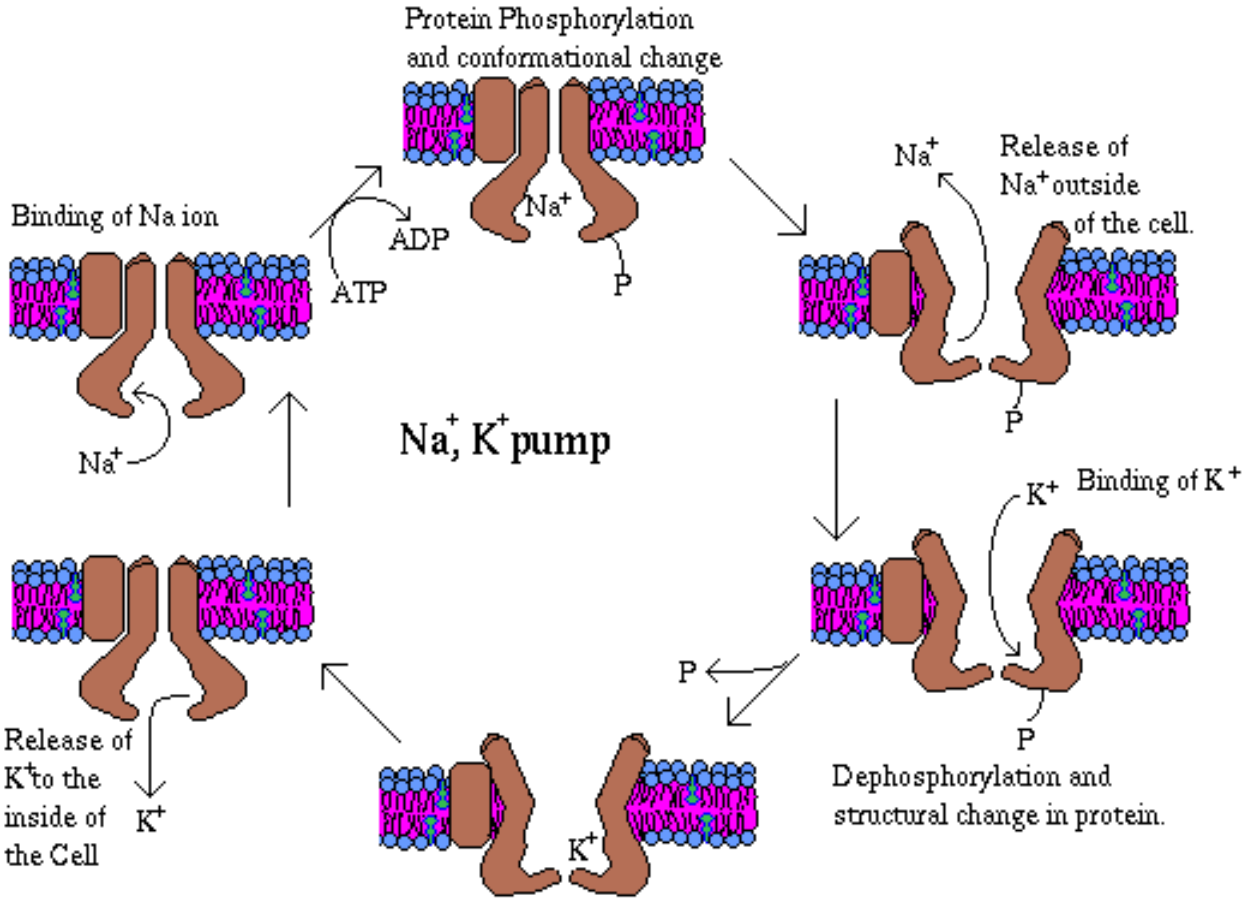
Fluid Mosaic Model

In 1972, Singer and Nicholson advanced a concept of membrane structure known as the "Fluid Mosaic Model."

It was this highly celebrated review article on the fluid-mosaic model of membrane structure that called the Attention of biologists to the importance of physical properties of membranes in regulating their physiological activities.


Outside cell
Glycoproteins
Phospholipid bilayer
Globular membrane proteins
Cytoplasm
Nucleus

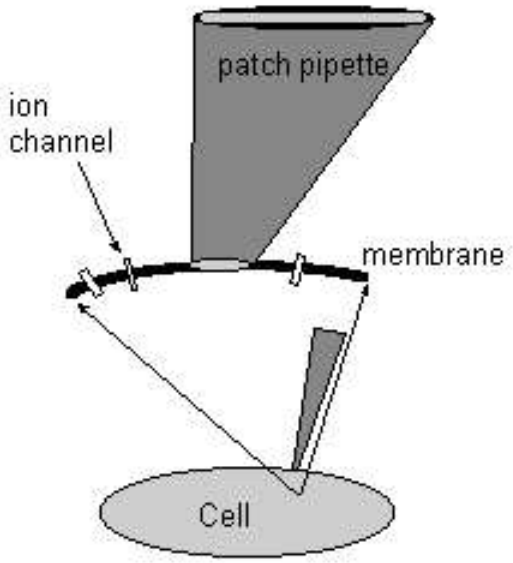
ATPase (The Sodium-Potassium ATPase pump)

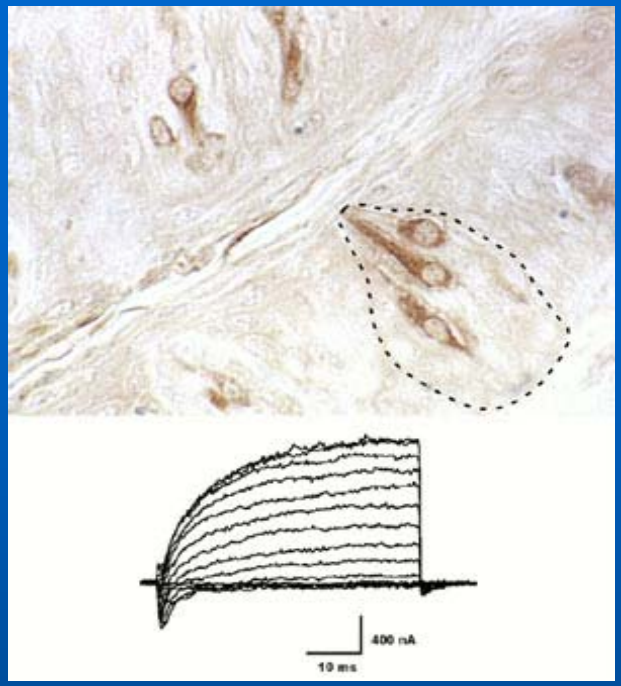


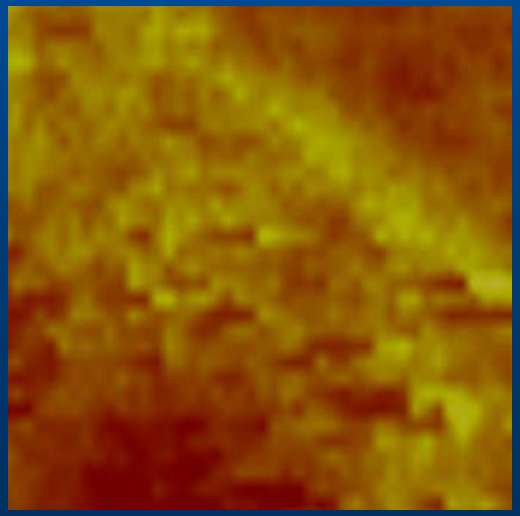
- The Top is the Outter membrane.
- The Bottom is the inner membrane (inside of the Cell)

The Patch Clamp Era

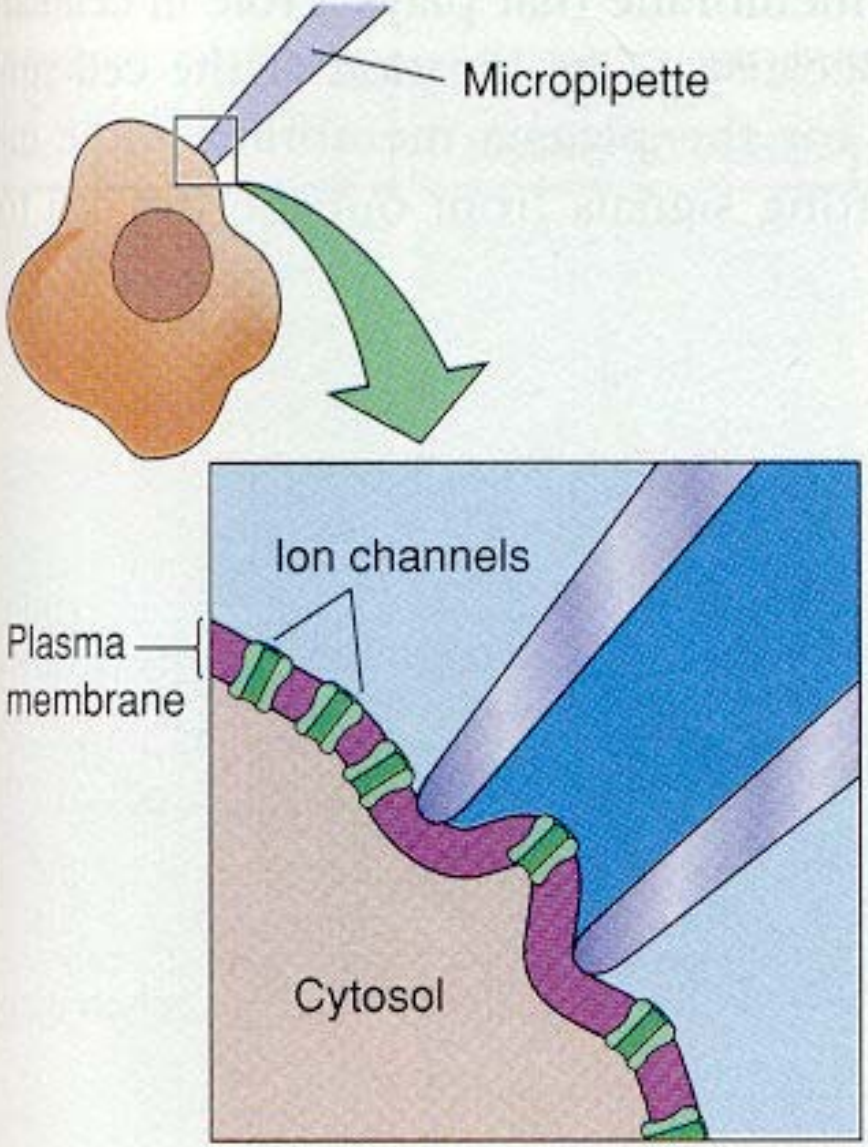
- Patch clamp is a basic science too developed some 15 years ago
- It won the developers (Neher & Sakman) The Nobel prize for Medicine in 1991
- Patch clamp has revolutionised our understanding of the role played by ion channels in health & disease

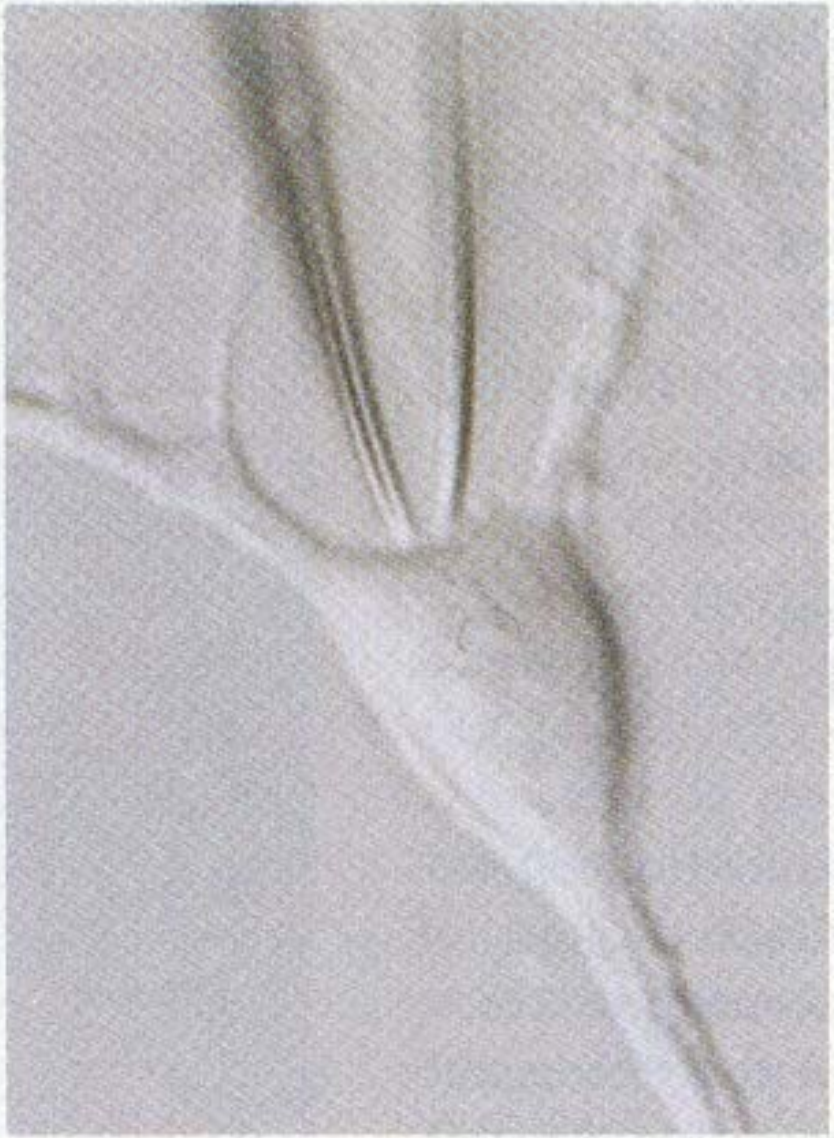


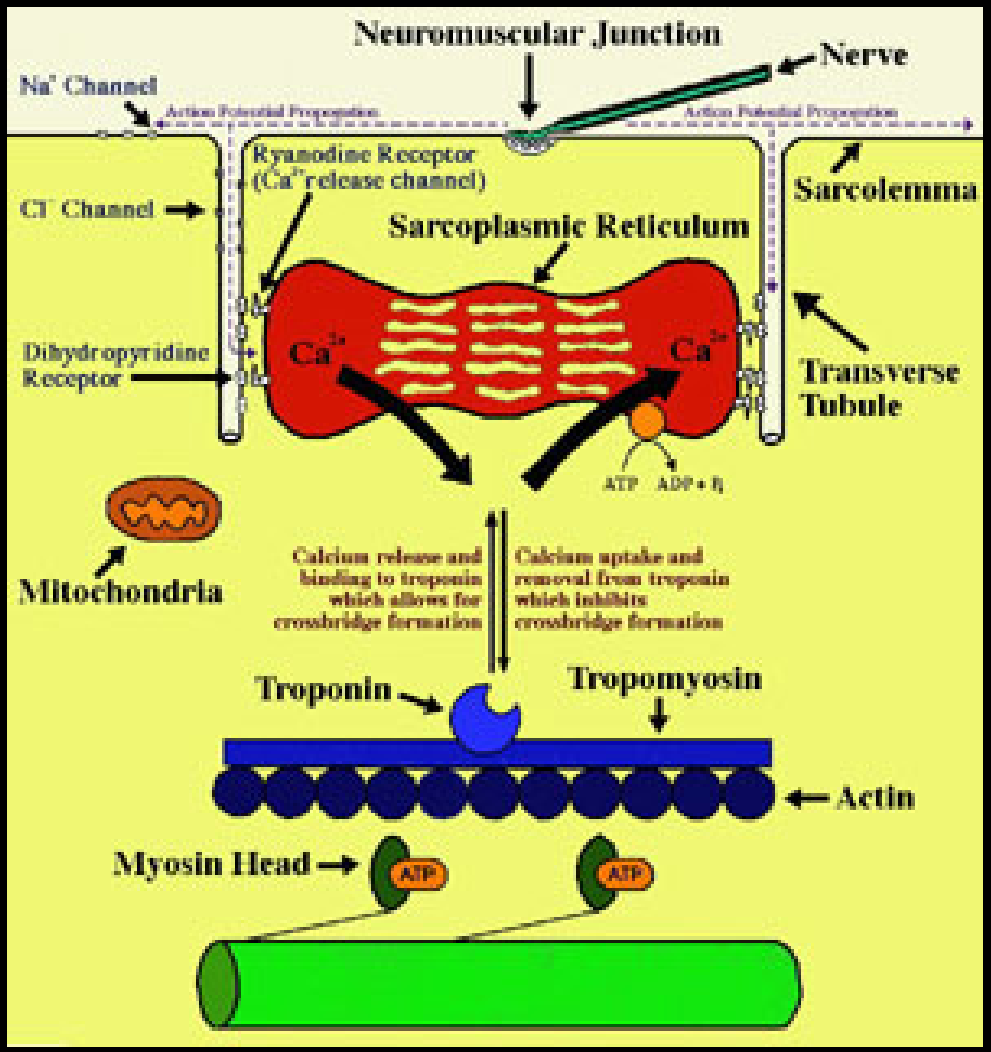


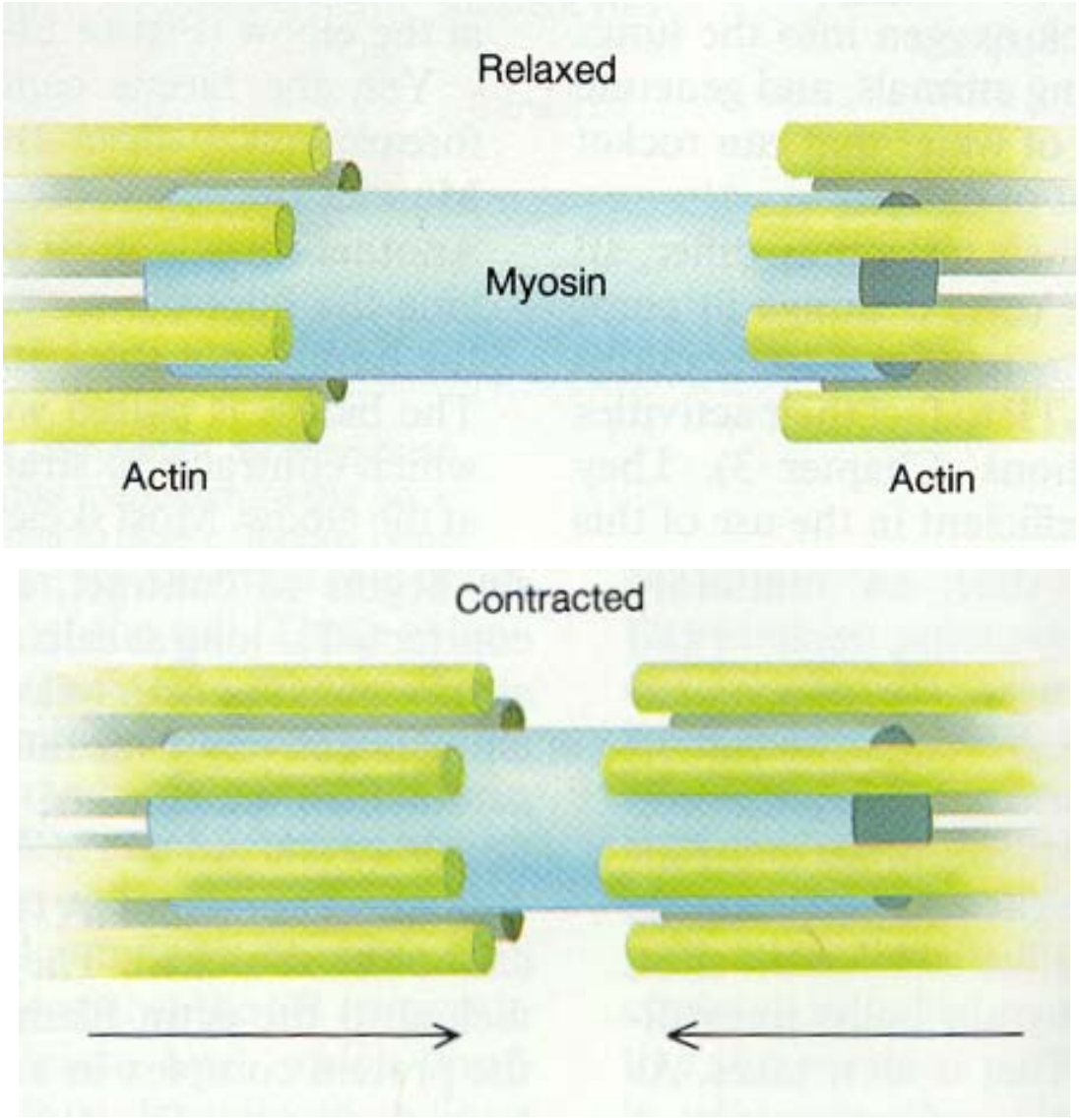


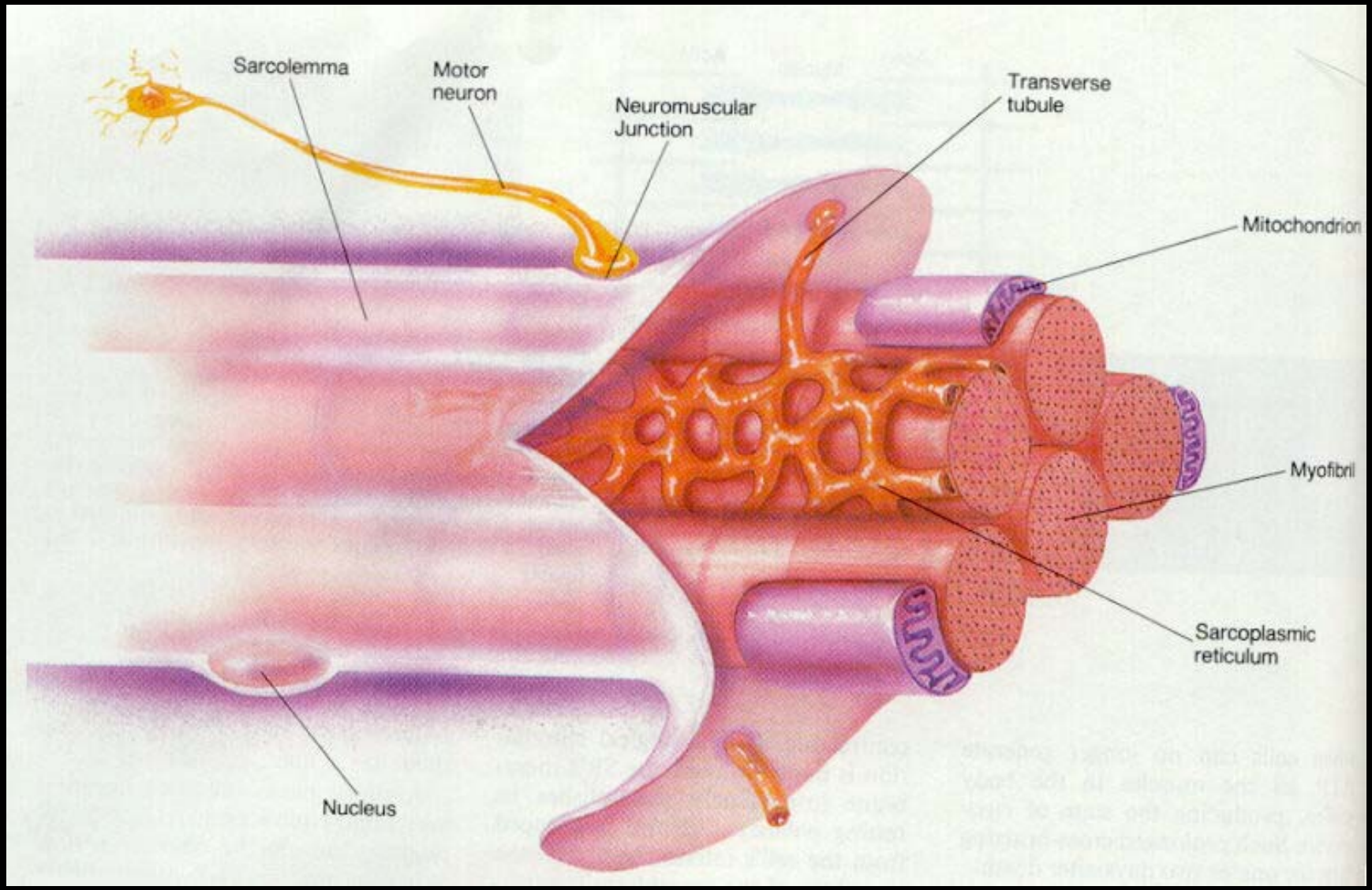
Elegant freeze fracture studies have demonstrated the presence of linear arrays of intra-membranous particles that are candidates for these calcium channels. To determine the organization of these specific proteins a selective labeling technique is required that can identify the location of individual calcium channels. Using biotinylated w-conotoxin GVIA, which binds selectively to calcium channels that stimulate neurotransmitter release, together with avidin-30nm gold particles, we have identified the location of calcium channels in an isolated nerve terminal with the atomic force microscope.

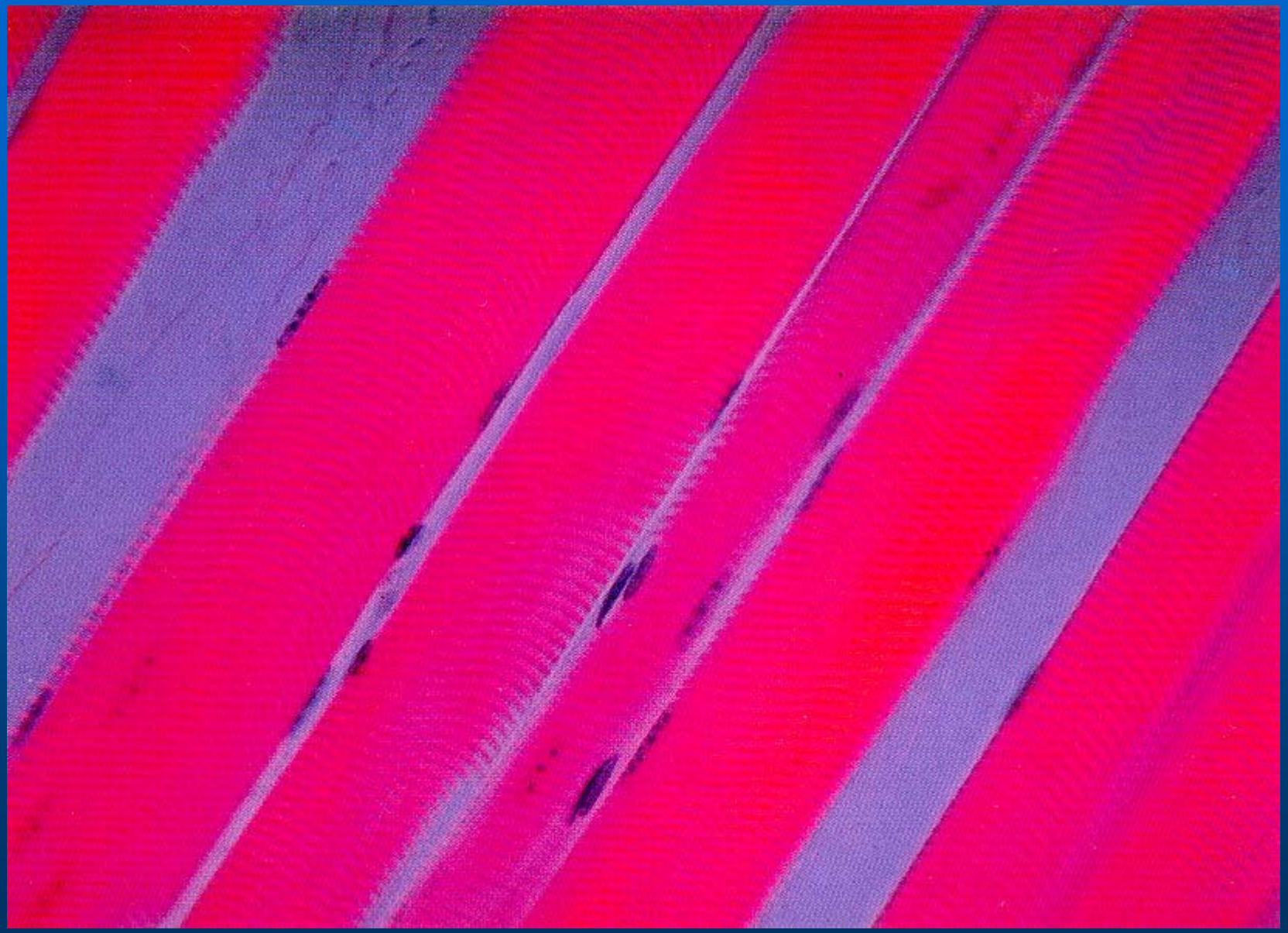

Micropipette
Ion channels
Plasma membrane
Cytosol

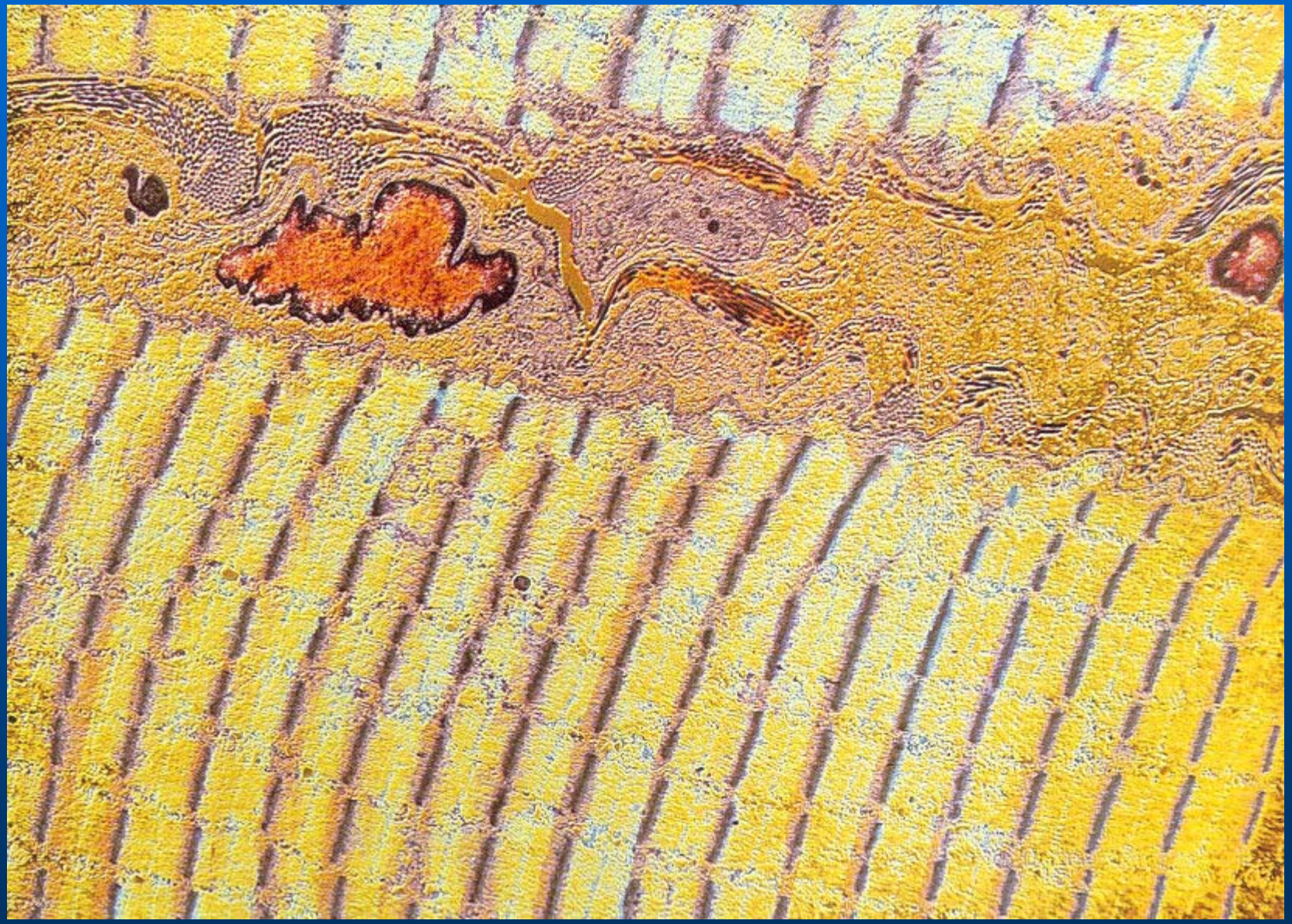


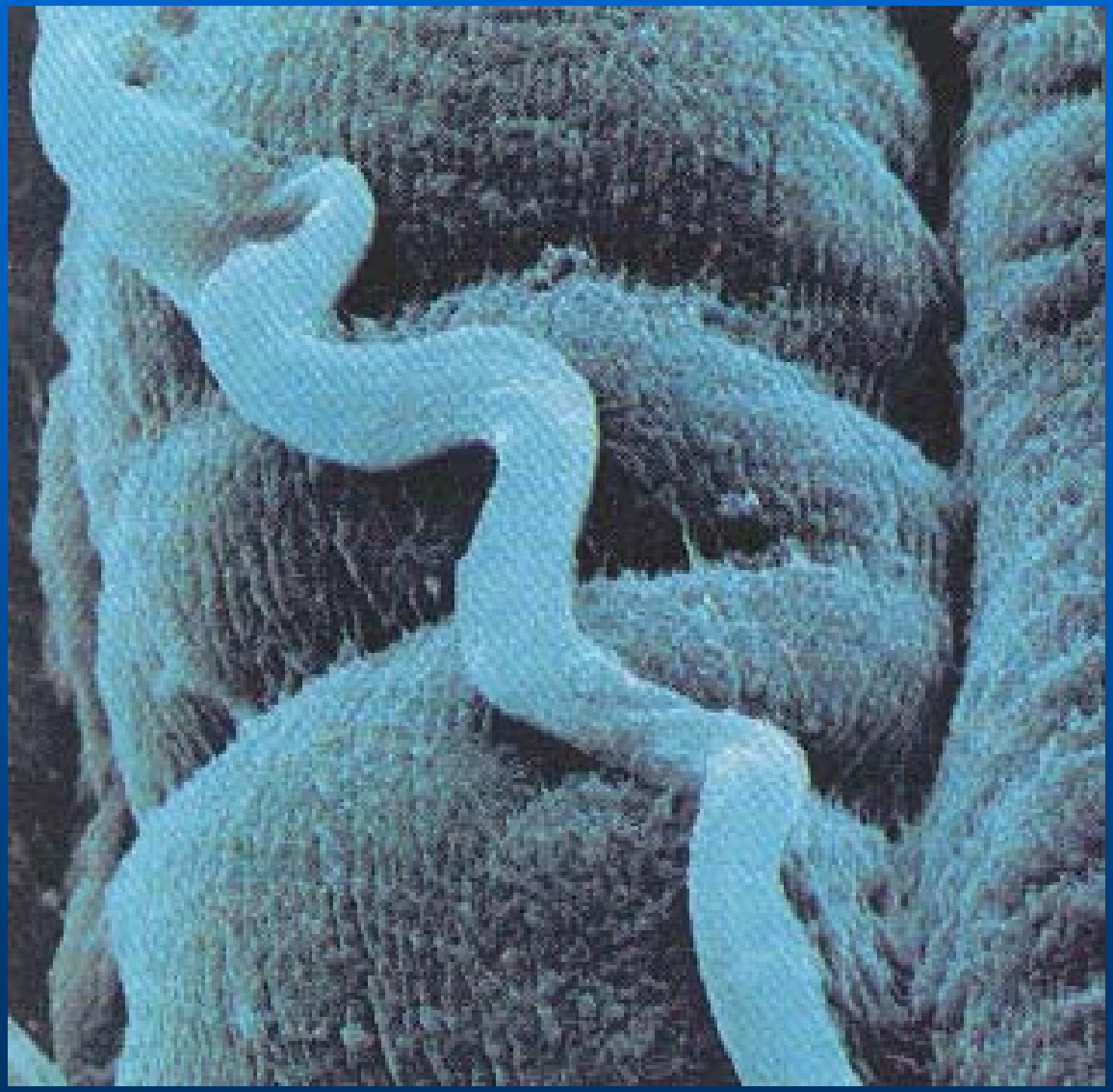

Neuromuscular Junction
Nerve
Na^+ Channel
Action Potential Propagation
Action Potential Propagation
Ryanodine Receptor
(Ca^{2+} release channel)
Sarcolemma
Cl^- Channel
Sarcoplasmic Reticulum
Dihydropyridine
Receptor
Ca^{2+}
Ca^{2+}
Transverse
Tubule
ATP
ADP + Pi
Mitochondria
Calcium release and
binding to troponin
which allows for
crossbridge formation
Calcium uptake and
removal from troponin
which inhibits
crossbridge formation
Troponin
Tropomyosin
Actin
Myosin Head
ATP
ATP

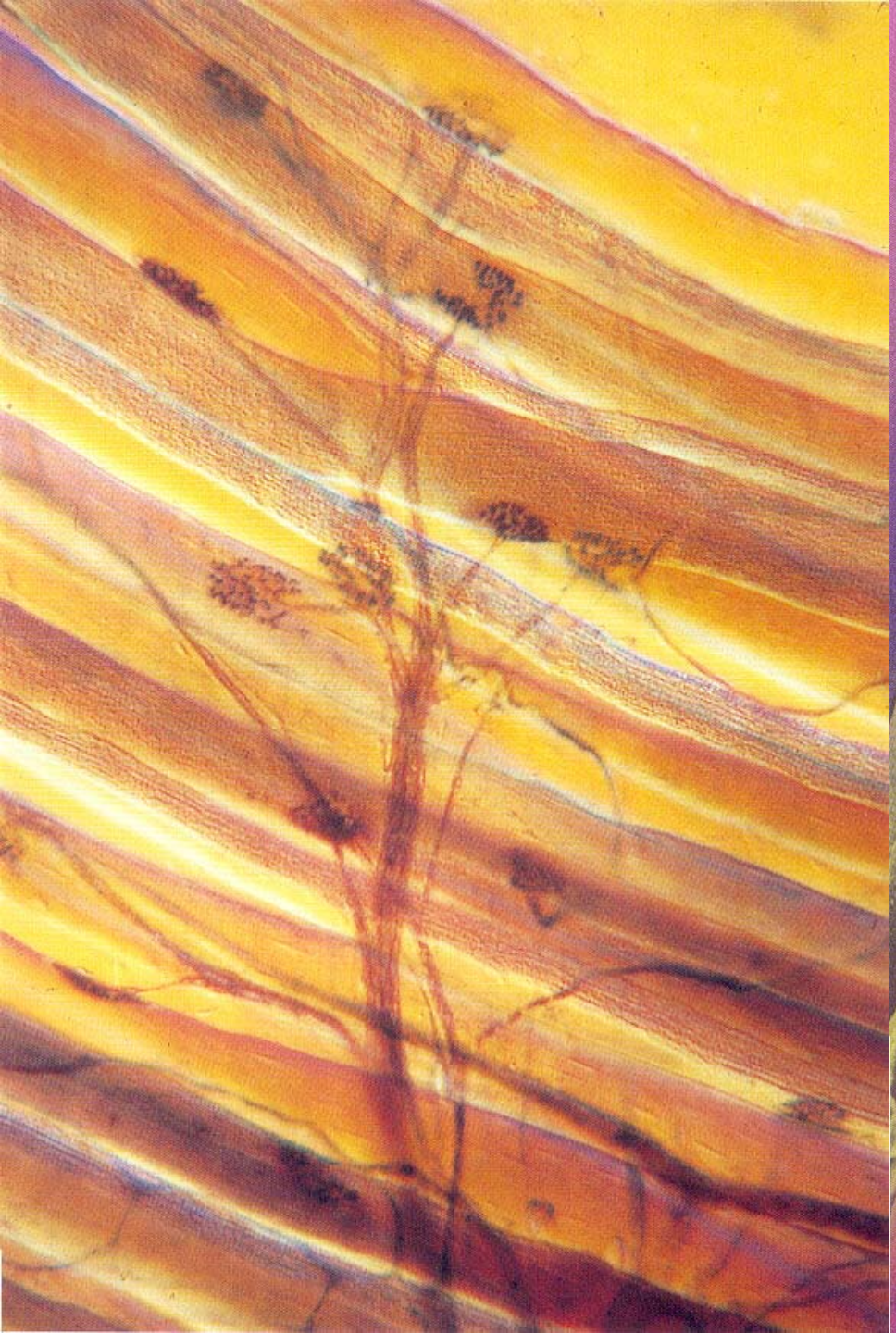

Relaxed
Myosin
Actin
Actin
Contracted

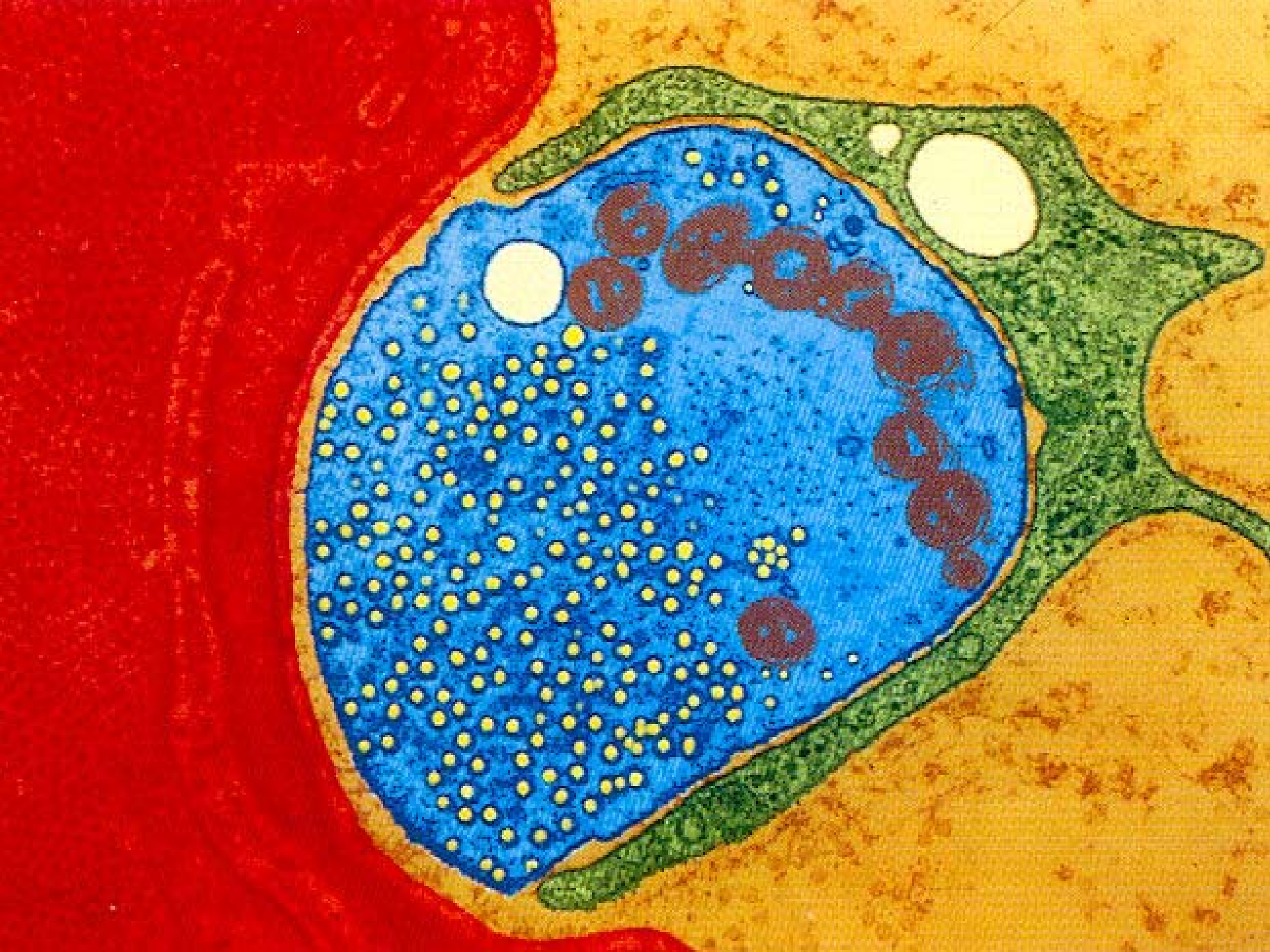

Sarcolemma
Motor neuron
Neuromuscular Junction
Transverse tubule
Mitochondrion
Myofibril
Sarcoplasmic reticulum
Nucleus

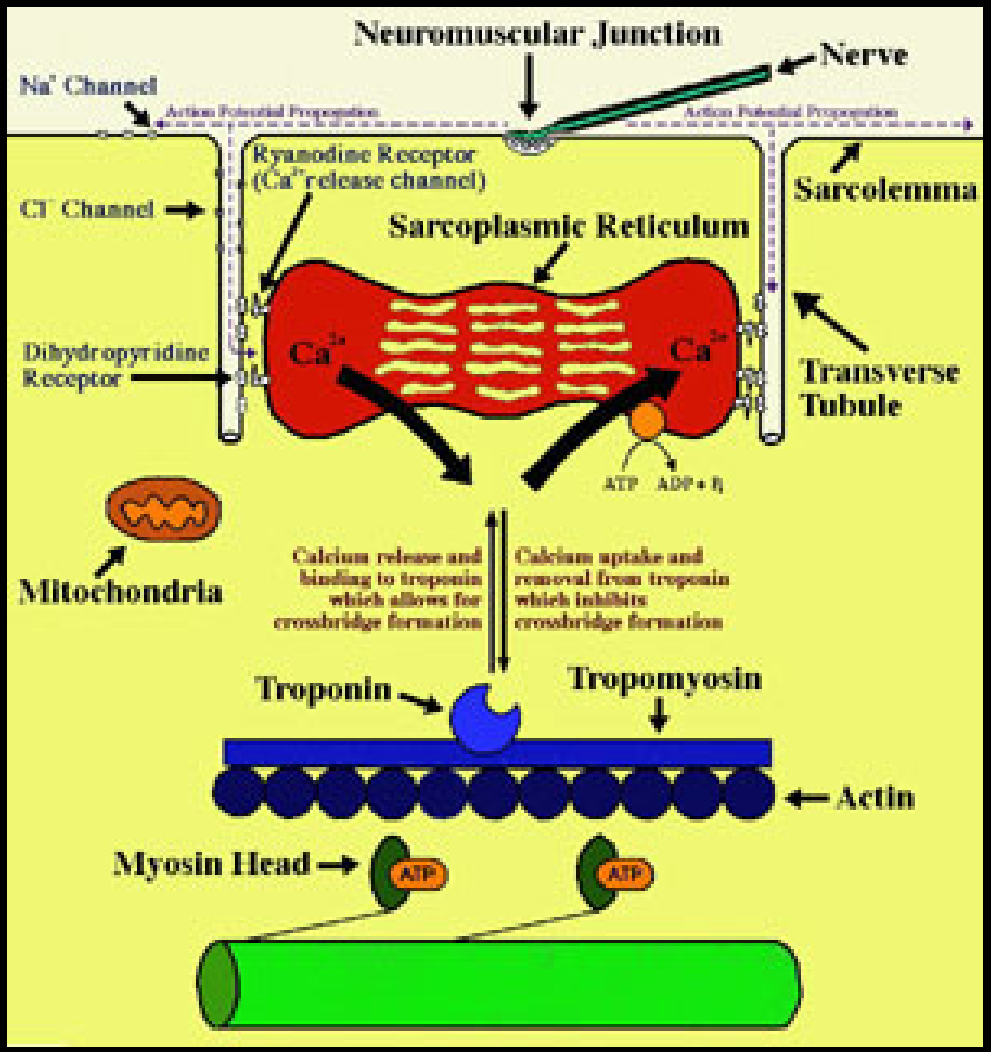











Neuromuscular Junction
Nerve
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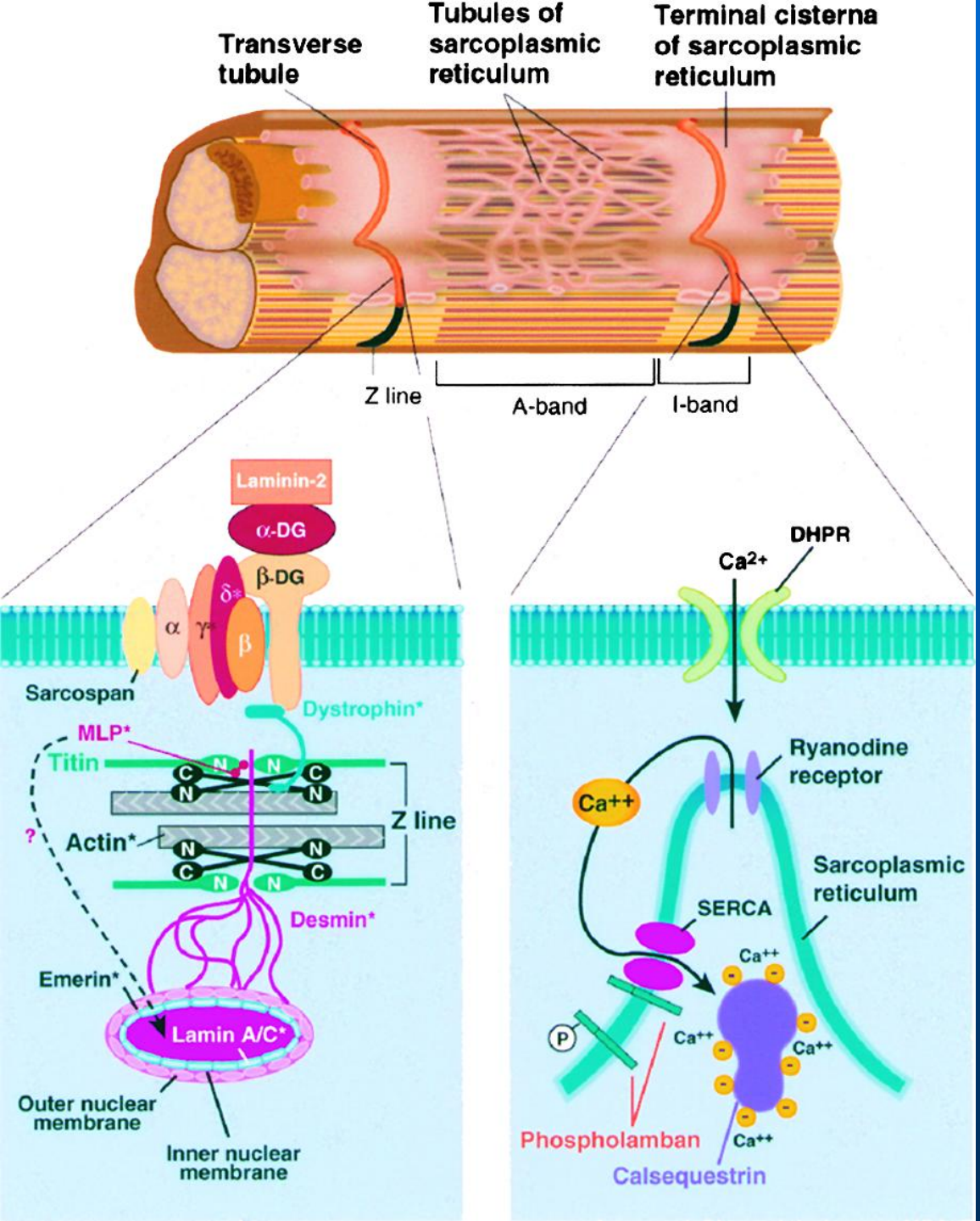
Ryanodine Receptor
(Ca^{2+} release channel)
Sarcolemma
Cl^- Channel
Sarcoplasmic Reticulum
Dihydropyridine
Receptor
Ca^{2+}
Ca^{2+}
Transverse
Tubule
ATP
ADP + Pi
Mitochondria
Calcium release and
binding to troponin
which allows for
crossbridge formation
Calcium uptake and
removal from troponin
which inhibits
crossbridge formation
Troponin
Tropomyosin
Actin
Myosin Head
ATP
ATP


Transverse tubule
Tubules of sarcoplasmic reticulum
Terminal cisterna of sarcoplasmic reticulum
Z line
A-band
I-band
Laminin-2
α-DG
β-DG
δ*
α
γ*
β
Sarcospan
Dystrophin*
MLP*
Titin
N
C
Z line
?
Actin*
Desmin*
Emerin*
Lamin A/C*
Outer nuclear membrane
Inner nuclear membrane
DHPR
Ca2+
Ryanodine receptor
Ca++
Sarcoplasmic reticulum
SERCA
P
Phospholamban
Calsequestrin

Milestones: The Big Picture

- Watson & Crick DNA Structure — 1953
- Hodgkin & Keynes Potassium "Channel" — 1955
- Frey & Edidin Fluid state of the cell — 1970
- Singer & Nicholson "Fluid Mosaic Model." — 1972
- Neher & Sakmann "Patch Clamp Technique" — 1976
- Hoffman, et al Confirm HKPP chrom. 17 — 1991
- Fontaine, Ptacek, et al HypoKPP chromosome 1q31-q32 — 1994
- Founding of PPA — 1997
- Mapping of the Human Genome — 2000
- Ptacek, Tawil, et al Andersen's Mutation Found — 2001

2002

October 2001 and Beyond!

Ask The Experts
PPA Research Registry
PP & Myotonia On-line Survey
Cooperative Research Projects
Science and Medical Advisory Board