Conversations on Cardiac Physiology

Conversations on Cardiac Physiology:

Heart Fallacies

By

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PREFACE

These conversations are examples of the types of conversations used in teaching and discussion with colleagues, and in explaining scientific thinking to nonprofessionals. They do not relate to any specific individuals or instances. I try to use this type of analysis to expose some popular ideas that turn out to be fallacious but appear in the literature and popular sources of scientific information such as Wikipedia and even the lay press (Figure 0.1). The excessive use of the phases, “scientists believe” or “I believe” spoken by one claiming to be a scientist, is quite inadmissible outside the studies of religion and theology.

INTRODUCTION

Figure 1. Press reporter, "Scientists now believe life started in volcanic vents the sea bed". Left: Professor, "If they use the verb, 'to believe', they are not scientists". Original private drawing by Prof AJ Drake Holland.

My dedication to Colin Blakemore is due to admiration for his stand against the anti-vivisectionists and his insistence that animal experimentation was essential if we wanted progress in physiology for the benefit of medicine. As for so-called 'animal rights', animals have one only and that is absolute and is the right that no cruelty shall be permitted, not only by scientists but by farmers, pet owners, and any others that rely on animals. We scientists have the help of ethics committees and supervision by Home Office Inspectors.

Heart must be one of the most frequently used words in English literature, but used to mean something else, e.g., love, feeling, thought, center, key etc. This book is about THE heart, a muscular organ in the chest that pumps the blood around the body. It is of obvious importance because, if it stops

beating, the body dies unless dramatic action is taken by doctors.

I assume that the reader and my students have learned the anatomy of the heart including that of its electrical conducting system. I try, in this book, to take a strictly scientific approach, strictly because there is a lot of so-called science that is not science in my opinion. That is because one cannot prove a theory (also called a hypothesis); one can only disprove it. Science progresses by such disproof, e.g., in the beginning people thought the Earth was flat; that is easily disproved by watching a sailing ship at sea proceeding to hull down and then go below the horizon, mast and all. That led to the sphere theory, then to the oblate spheroid theory [Asimov, 1989], and now, to theories based on images of the Earth from outer space. However, these still depend on the method used to acquire the data, so disproof is still possible. The big bang is still a theory not proven.

All one can do is perform experiments and collect data that attempts to disprove the hypothesis of interest. The data cannot support a hypothesis; it can only be consistent with the hypothesis. Unfortunately, some people tend to cling on to disproved hypotheses. If a person like this has great influence, it is very damaging to the progress of science, e.g., the Pope punishing Galileo for disproving the theory that the sun orbits the Earth. This still happens in the science of heart function by leaders of opinion getting on to grant giving committees and editorial boards. Thus, the subject acquires fallacies that people believe in; the verb “to believe” has no place in science. Some theories in biomedical science are of more fundamental importance than the heart fallacies that I will describe in this book. Pretty much all of us subscribe to the idea of evolution resulting in new species [Darwin, Origin of Species by means of Natural Selection, 1859]. Remarkably, there is still controversy about how superior or inferior natural selection takes place. At present, according to Wikipedia, following Haldane [1933], “an organism's DNA affects how it looks, how it behaves, and its physiology. So a change in an organism's DNA can cause changes in all aspects of its life. Mutations are essential to evolution; they are the raw material of genetic variation. Without mutation, evolution could not occur.” This is wrong. Mutations cause a sudden change in the genome and are harmful. A famous example is the appearance of haemophilia in the genome of Queen Victoria, which was passed on to some of her descendants, notoriously including the family of the Romanov Tzars of Russia! Evolution is not like that. As Darwin observed, there are gradual changes from generation to generation as useful characteristics become more advantageous (humans become taller, straighter and more athletic with world records regularly being broken, while useless characteristics like the human appendix become shriveled and

functionless, called vestigial structures). Denis Noble [2022] (not a relative of mine) explains this as entry into the genome of acquired characteristics. We need to ditch the mutation theory and test other theories, of which Denis Noble's seems to be a good candidate.

In addition, in rejecting the concept of evolution by mutations, it is necessary to reject the concept of the cytosol. The cytosol is supposed to be a liquid solution that fills the interior of living cells. This should never have been adopted in the first place because the old physiologists of the 19th century simply squeezed out the contents of cells and obtained jelly like material a gel. This is due to the structured nature of intracellular water [Pollack, 2013]. In biology and medicine, the first thing investigators wanted to know was the anatomy. In recent times, magnetic resonance imaging (MRI) has improved anatomical accuracy and enabled it to be studied in living material and patients. This is only possible if the water in the object of study is structured as suggested by Pollack who acknowledges that the idea came from Gilbert Ling, who was much derided by the opinion leaders (he could not be always correct. [Ling, 2001]). MRI depends on intracellular structured water, the cytoplasm, to map the structure of soft tissues; it would not work if the cell interior was cytosol.

The present book tries to draw attention to scientific fallacies of the heart with regard to normal function (physiology) and disease (cardiology). I will not touch much on the circulation because I have already done so [Westerhof, et al., "Snapshots of Haemodynamics", 2019]. I will only partly touch on electrophysiology because I have written on that subject in greater detail [Noble, "Electromagnetism of Living Cells", 2021]. However it should be mentioned that the first of a series of papers emphasizing the major role of electricity in nature has been published [Funk and Scholkmann, 2022] it is suggested that the reader follow subsequent articles in this series.

In order to illustrate the sort of problem I have with wrong beliefs, I give an example from a noncardiac subject. The hypothesis that we wanted to test was whether the airway resistance changed in acute left ventricular failure. Lung doctors assess airway function by asking subjects to blow as hard as they can into a tube and measure the flow and volume of expired air through the tube. It should be obvious that one can get any data one wants depending on how much effort the subject puts into the maneuver. It is not practical to ask patients in acute left ventricular failure to perform this maneuver, as they are so weak. However, it has been known for many decades that the airway resistance can be measured with the subject just breathing normally in and out of a tube, by oscillating the air in the tube and measuring the

pressure and flow (more recent confirmations are found in Snashall, et. al. [1991], and Ahmed Al-Jumaily, Lulu Wang [2022]. But doctors persist in using the forced expiration method. The usual excuse for this sort of thing (disappearance of diagnostic tests that were of proven value in the past) is cost. I think that nevertheless there are plenty of examples of "clinging to the old idea" that abound in texts on heart physiology and medicine, of which some increase health costs.

In summary, I would say that my philosophy of science is close to that of the great physicist, Richard Feynman [2011], who explains the role of physics in other sciences. The poor philosophy of the "clinging to the old idea" is very well described and condemned by Feynman [1992]. He says, in effect, one should have a guess at how something works, test it and if it does not work out, abandon the idea and start again. It is Feynman's precepts that I have tried to follow. This is very close to the philosophy of Karl Popper [1963], who states that theories have the property of "falsifiability".

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CHAPTER 1

THE ELECTRICITY OF LIFE

Fallacy 1: Cell trans-membrane electric potential depends on the distribution of sodium and potassium ion concentrations outside and inside the cell. WRONG.

Introduction

As a Professor, I used to regard my primary role as that of a teacher. I encountered many different types of students. One extreme type was those with large memories who could read the literature, pass the exams easily and become first class doctors. At the other extreme were those less confident, that were not so good at memorizing things but were capable of embarrassing the professors by asking questions that they could not answer. These tended to be superior at research. I present imaginary dialogues with this kind of student to show up why some accepted theories may be wrong.

Professor: What is the electrical voltage within a living cell?

Student: I think it is negative.

Professor: That is the universal convention, but it is a convention adopted by the pioneers of electricity discovery and research. It is not now appropriate in my opinion, as electricity is now defined by the Systeme International [Noble, 2019] as “electrons moving”. That inappropriateness does not matter in human application of electricity, nor indeed in its cardiological applications, but it makes a huge difference to the answer to my question.

Electrons are both subatomic particles that form the outer (valency) orbit round the atomic nucleus and are also an electromagnetic wave. Arbitrarily giving them a negative sign does not work when considering organic chemistry and cellular activity. Electrons differ from photons in having a tiny mass. The mass of the electron is $9.10938215 \times 10^{-31}$kg. Protons have about 1000 times more mass and sodium ions are about 10,000 times greater in mass. You will realize that, by Newton's second law, for a given

electromotive force, electrons will accelerate 1000 times more than a proton and 10,000 times more than a small ion.

Student: but why does this make the intracellular voltage not negative? I thought that the negativity was caused by the balance between the inside and outside concentrations of sodium and potassium ions.

Professor: That is the conventional explanation. Its advocates quote the Nernst equation or rather an adaptation of the Nernst equation applied to ions (the original equation did not). The essence of the ionic version of the equation is that the intracellular potential depends mainly on the ratio of extracellular to intracellular potassium ion concentrations, $[K^+]$. The extracellular $[K^+]$ is about 4mM (4 millimolar) compared to about 100mM inside the cell [Milo and Philips, 2020]. Most important, the distribution of potassium ions between extracellular and intracellular compartments of a number of living cells in the same organism was found to be constant.

Student: Then the intracellular electrical potential of these cells should be constant.

Professor: But it is not. The measurements are:

Table 1:1

Tissue	Trans-membrane Electric Potential (mV)
heart ventricle	-85
skeletal muscle	-80
vascular endothelium	-80
nerve	-80
adrenal cortex	-70
leukocyte	-65
salivary gland acinar cell	-65
sinus node cell	-60
vascular smooth muscle cell	-60
platelet	-56
brown fat cell	-54
retinal cell	-40
pancreatic acinar cell	-39
liver	-37
fat cell	-34
pancreatic islet cell	-22
red blood cell	-9

My attempts to state that this data disproves the Nernst ion balance theory for the determination of the voltage within living cells [Noble MIM, 2020] has been largely ignored.

Student: So you think that theory is disproved?

Professor: Yes

Student: So what do we do now?

Professor: Get rid of this inappropriate negative sign on the electrons. The same problem arose in Scudder's study of organic chemistry [Scudder, 2013] which is full of electron flows, e.g., in photosynthesis and all other metabolic organic synthetic processes; valency is also dependent on the sharing of electrons.

Student: How can you do that?

Professor: I calculated the mean square of the potential, which changes the minus to a plus. Scudder showed that electrons flowed from one location to another when there were more electrons in the first location, and fewer in the second location. This does not follow Ohm's Law if the electron is negative but is the equivalent of Ohms Law if the electron is positive. Electrical resistance of the intervening material between the two locations can then be calculated. Scudder used the term, electron density for the "positive" electrons.

Student: Why density?

Professor: Electron density is defined as the *probability* of an electron hitting your measuring electrode. This is because the electrons are buzzing around all the time; it's not like the voltage you would record from a man-made battery.

Student: How does this help you to a new theory of the electricity of living cells?

Professor: Before I retired, I earned my living as Prof of Cardiovascular Medicine involving interpreting hundreds of electrocardiographs (ECGs), an essential part of making a heart diagnosis. This can be done without worrying about the theoretical considerations we have discussed, by using a good reference like Pulak Sahay's [Sahay, 1996]. But after I retired, I had time to think, and as I knew that one can record voltages virtually all over the body surface, it dawned on me that the body itself was *generating* the electricity.

Student: So, the heart itself generates the electricity that causes the ECG?

Professor: Exactly, you've got it.

Student: How?

Professor: It had to happen within the individual cells, as a consequence of the variety of results of penetrating different cells with microelectrodes as in the table above.

Student: Where in the cell?

Professor: That is very difficult to investigate, so I looked for measurements of voltage in the different organelles of the cell, and found the data in Table 1:2 ([Noble MIM, 2020])

Table 1:2

Organelle	Electric Potential (mV)
lysosome	19
endoplastic reticulum	0
nucleus	15 more than cytoplasmic
mitochondrion	-180 to -220

I then assumed that, as the mitochondria had the greater electron density, which was the most likely site of electron generation. The lower electron density of the cytoplasm could be attributed to the resistance of the mitochondrial membrane.

Conclusion: Intracellular electricity is generated within the cell and is not related to the distribution of sodium and potassium ions.

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CHAPTER 2

CARDIAC NATURAL PACING

Fallacy 2: The pacemaker current is a "funny" electrically positive inward current in the sinus node cells. WRONG.

This chapter accepts that early in evolution there was a division, more or less, between plants and animals although, as will be revealed, some processes are common to both. Here, we concentrate on the consequences, in most animals, of locomotion in order to obtain food. One of these consequences would have been the need for an internal distribution system for nutrients, waste material and dissolved gasses. For this function, we know, through Harvey's work [Harvey, 1628, 1653] that, in the animals most familiar to us, and in ourselves, natural selection must have selected a beating pump designed structure. However, for regular beating, there must be a control system, i.e., a pacemaker. Activation of cells is brought about by a loss of internal voltage (in this case activating a heartbeat with an action potential (systole) which must be followed by restoration of the voltage (diastole) to be ready for the next beat. The conventionally taught mechanism of this cycling is explanation in terms of ion flows carrying electric currents. One feature of this approach is the postulation that a positively charged current flows slowly inward after an action potential until it reaches a "threshold" (involving a calcium ion (Ca^{2+} flow) which triggers the next action potential. This inward current is named "funny current" (If) because nobody can find an ion to carry it. To my way of thinking, the widespread literature about the "funny current" is fundamentally unscientific, when there is a perfectly reasonable explanation in terms of electron outflow.

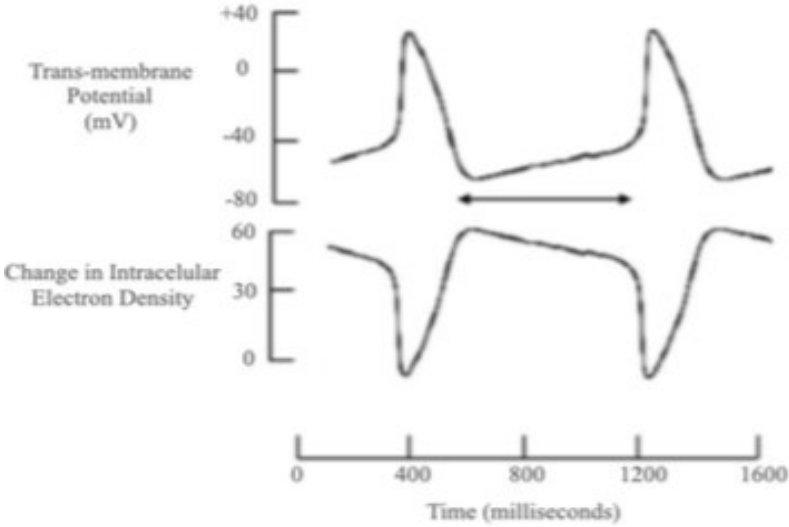

Figure 2:1. Sino-atrial node (SAN) natural pacemaking. Top trace: Intracellular voltage of sinus node cell recorded conventionally. Diastolic pacemaker current occurs during the time indicated by the double arrow. Bottom trace: Inverted signal to indicate the decline in electron density produced by an outward flow of electrons.

*The top trace shows how the conventionally recorded SAN intracellular voltage drifts to a less negative value between action potentials (double arrow), until it reaches a threshold to fire the second action potential. The lower trace shows how, during the same interval, the cell is losing electrons. Reproduced by permission from Figure 9 in Noble, Mark IM [2021] [*Electromagnetism, Quanta, and Electron Flow in the Electrophysiology of Living Cells*] [London]: [World Scientific Publications].*

Professor: We have already agreed that the heart beating is essential for the continued life of an animal. What is the evidence that this is spontaneous and not controlled?

Student: I suppose that, as it can go faster, it is controlled.

Professor: You are correct in that sense but if you remove the heart, or denervate it or transplant it, it goes on beating [Noble et al, 1972].

Student: Oh yes; I have watched another professor set up a Langendorff preparation [Bell, Mocanu and Yellon, 2011].

Professor: Yes, unlike skeletal muscle which is paralysed if you cut the motor nerve; what keeps the heart contracting?

Student: There is an automatic pacemaker in the sinus node.

Professor: Do you know how it works?

Student: Something to do with a pacemaker current.

Professor: Yes, but the DiFrancesco group [1980, 1986] were fixed on the concept of positive current and thought that the drift in voltage (from -60 to -40mV) between beats, which triggers an action potential at -40mV (the threshold) was evidence for an inward current carried by positively charged ions.

Student: I suppose that would work.

Professor: Unfortunately, neither they nor anyone has found the ion, so they called the supposed inward current, the funny current with the symbol If.

Student: No. Professor, you can't possibly have an imaginary "funny current"!

Professor: Quite correct. There is no inward positive current between beats.

Student: What is happening then?

Professor: A simple ordinary current, which is outward, carried by electrons. The electrical resistance of the cell membrane gets lower the lower the trans-membrane potential. At electron density +60 mV, the resistance is insufficiently high to stop a slow outward electron flow. When the transmembrane potential gets down to electron density +40mV (the threshold), an action potential is triggered.

Student: How do you measure that?

Professor: I simply invert the recording of voltage see Figure 2:1.

Student: What evidence have you that it is electrons whose flows constitute the pacemaker current?

Professor: Simple. Injecting electrons shortens the diastolic interval: withdrawing electrons lengthens the diastolic interval [Jaliffe et al., 1980].
Student: How does the heart rate increase with exercise and stress?

Professor: We know that the sympathetic nerves (autonomic, efferent) release nor-adrenaline (same as nor-epinephrine) which acts upon adrenergic receptors on the sinus node cell membrane. Similar, but slower in onset, is the same mechanism when adrenaline (same as epinephrine) arrives via the circulation from the adrenal gland. I have found no clear agreed explanation of the molecular mechanism; the literature seems to get all tied up with pathological tachycardias.

Student: I should have thought you would have a theory!

Professor: I have certainly thought about it, and have produced the hypothesis that the end effect is to lower the electrical resistance of the cell membrane, so that, for the given electron density between the cytoplasm and the exterior, the electron flow is faster and the time to reach the threshold electron density of 40mV is shorter. A shorter time between beats means a faster heart rate.

Student: But I want to know how the stimulation of the adreno-receptor causes this lowering of electrical resistance of the cell membrane.

Professor: A very worthy ambition, but I am confused about it. You need to ask one of those much cleverer professors who know all about molecular pharmacology. I hazard a guess that they will not have considered an effect on electrical resistances.

Student: Perhaps I could do research on that?

Professor: I suggest you find a group who measure sinus node electrical events, and a group that know what the metabolic end-product of adrenergic receptor stimulation is and observe the effect of this product on the electrical recordings in the sinus node. That would be a good search, hopefully not needing research.

Student: Phew!

Professor: Yes. Collaborative research is very difficult, but the most effective and rewarding.

Student: And I suppose you're going to produce something opposite to my last question; this time it is to answer my question, "How does stimulation of the vagus (para-sympatheric) nerve, and acetylcholine, slow the heart rate?"

Professor: As you predicted; acetylcholine, whether released from parasympathetic nerve endings, for which it is the neurotransmitter, or whether injected, may increase the electrical resistance of the sinus node cell membrane, delaying the arrival of the pacemaker electron flow and arrival at the electron density at the threshold value, and therefore slowing the heart rate.

Student: That would seem to be a useful way of treating tachycardia.
Professor: Yes, in theory, but it is very difficult practically, so we used to just block the adrenergic effects, but there is now a drug that somehow slows the pacemaker current, namely Ivabradine. I think it may increase cell membrane electrical resistance to achieve this, but the literature is confused by the claim that it inhibits the "funny current" [Yael Yaniv et al., 2021].

Conclusion. The pacemaker current is a diastolic outflow of electrons and not an imaginary positive ion inflow

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CHAPTER 3

DEPOLARISATION AND REPOLARISATION DURING ACTION POTENTIALS

Fallacy 3: The sharp fall in intracellular electric potential during an action potential is caused by an inward flow of sodium ions. WRONG.

This chapter argues that for the loss of internal voltage during the upstroke of the action potential (depolarisation) in cells to be due to sodium ion (Na^+) inflow, too much Na^+ would move into the cell to be removed by the Na^+/K^+ATPase (sodium pump). The pump is only adequate to remove the Na^+ entering via the sodium/calcium exchanger (NCX). The fact that land plant cells also depolarize upon activation shows proof that it is not due to Na^+ inflow because sodium is toxic to such plans and kills them. By contrast, the electron outflow theory of depolarization can be applied to both plants and animals and is therefore a more likely universal feature of the living cells of Nature. Repolarization (restoration of trans-membrane potential at the downstroke of the action potential) has a more complicated explanation in conventional theory. This can be overcome by the hypothesis that this is due to generation of "new" electrons.

Student: In the last tutorial you described how when sino-atrial electron density declined to 40mV in diastole, there was a threshold resulting in an action potential to trigger the next beat. What I want to know is the mechanism of that threshold.

Professor: An action potential involves loss of intracellular voltage followed by its restoration. It turns out that calcium ions (Ca^{2+}) are involved in sino-atrial cells [Hagiwara et al, 1988], and I do not want to discuss that until I come to that big subject for the whole heart, but make sure I do address it.

Student: How can you address the phenomenon in that case?

Professor: Ca^{2+} is involved in all tissues that contract, so I look at something that does not contract e.g., a nerve axon. I should explain that in the 1960's, I did a PhD in Physiology, and, when attending meetings of the Physiological Society, I met those very great physiologists of those times, Hodgkin and Huxley who had done wonderful experiments on squid giant axons. Passing a positive electric current into the fiber required the presence of sodium ions (Na^+), whereas passing such a current out of the fiber required the presence of potassium ions (K^+).

Student: That is famous and frequently quoted.

Professor: Yes, richly deserved. Unfortunately, in my opinion, those particular findings (they achieved much more individually) have been ill used in the interpretation of natural spontaneous function. The conventional interpretation is that depolarization (loss of intracellular electrical potential) is achieved by an inward current carried by Na^+ and its restoration by an outward current carried by K^+.

Student: Yes, that's what we're expected to say in the exam, but we also have to say that the increase in intracellular Na^+ concentration and decrease in intracellular K^+ concentration is corrected by the sodium pump.

Professor: Is it?

Student: I don't think you would ask that question if you thought so!

Professor: The sodium pump is a mechanism in the cell membrane, correctly called the Na^+/K^+ATPase, i.e., it is enzyme with splits ATP in order to expel $\mathbf{3Na^+}$ from the cell by admitting only $\mathbf{2K^+}$ into the cell, a skewed Na^+/K^+ exchanger.

Student: What's wrong with that?

Professor: You have too much Na^+ expulsion or too little K^+ restoration or both.

Student: Oh dear! That's not a steady state that natural selection demands.

Professor: Quite. But that is not the only problem. ATP splitting uses up energy, which natural selection would seek to minimize.

Student: Has anyone worked out how metabolism deals with that?

Professor: The much-derided Ling tried and concluded, "the result showed that the minimum energy needed for the postulated sodium pump is at least four times higher than, or 400% of the maximally available energy to a muscle cell, even if: (1) the muscle spends all its energy on pumping sodium, and even if: (2) all the essential energy conversion and utilization processes operate at 100% efficiency" [Ling, 1952, p. 766767, Figure 4].

Student: Do you believe him?

Professor: Do **NOT** use the verb "to believe" in science. Actually, I am not competent or qualified to judge the accuracy of his calculations. My instructions from my superiors are that anything Ling says is false, so it is false and do not breathe a word of it in a class or in an exam.

Student: Sounds like physiology is a dictatorship.

Professor: Certainly not; there is completely free speech. Ling is probably mostly wrong and sometimes right. You decide. However, from where we are now, there must be a bigger problem about electrolyte physiological balance in the steady state when Ca^{2+} is also involved, and the difficulties will be realized in future tutorials.

Student: In the meantime, what alternative do you propose to obtain an electrolyte steady state?

Professor; Simply, for action potential depolarization, the same solution as for diastolic depolarization in sino-atrial cells (previous chapter). I suggest depolarization is due to an outward flow of electrons. That does not involve moving ions out of place; it is a result of the principle that electrons move from a high electron density site (cytoplasm) to a lower one (extracellular space).

Student: And I suppose you favor that because electrons are faster movers than sodium ions?

Professor: Sure. Accelerating 10,000 times faster, achieving a speed of 430 volts/second [Berecki et al, 20010].

Student: And what about almost equally fast repolarization to complete the action potential in nerve axon?

Professor: We have a large electron density difference between mitochondria at 200mV or more to the cytoplasm at zero after emptying

during depolarization. Therefore, I postulate that electron flow from mitochondria to cytoplasm is the mechanism of repolarisation.

Student: What is the electrical resistance of that pathway.

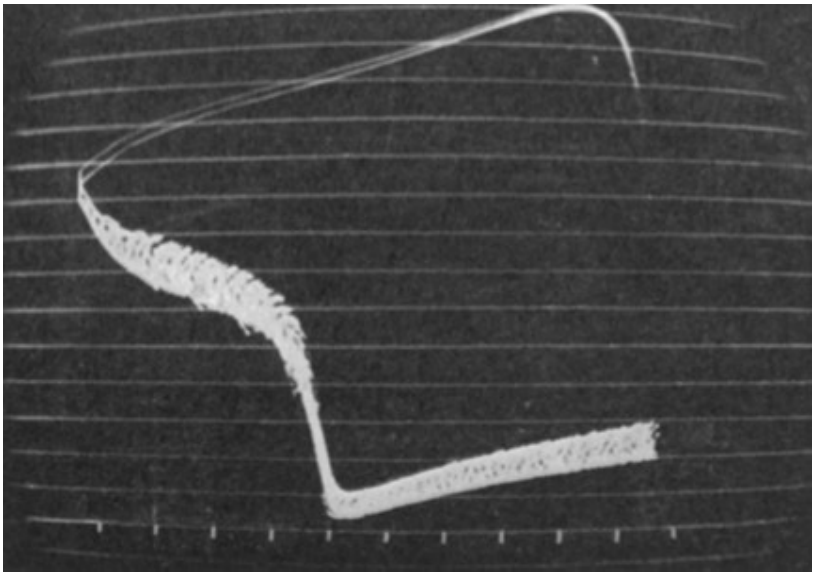

Figure 3:1: Cathode ray oscilloscopic tracing from intracellular electrode of a Purkinje fiber obtained by Silvio Weidmann [1951]. The Y axis is voltage; the horizontal lines are 10mV apart. The X axis is time, with the markers 100 milliseconds apart. Superimposed on the action potential are the effects of applied fixed amplitude intermittent electron currents causing vertical thickening of the action potential trace. Thickness at fast upstroke = too thin to discern. Thickness during plateau = greatest, indicating maximum electrical impedance. Thickness during diastolic pacemaking is less than during plateau, indicating impedance insufficient to prevent some outward electron flow. Thickness during repolarization = minimum after upstroke, indicating impedance sufficiently low to allow inward electron flow (repolarization). The thin lines at the top are caused by the oscilloscope back sweep. From Weidman [1951], Weidman known to author but deceased at the time of writing this book.

Professor: There is a lack of data on that, but there is a very nice paper by Silvio Weidmann [1951] (Figure 3:1), who correctly called his measurements impedance (that includes inductive, capacitance and semiconductor contributions to the opposition to electron flow) but is nevertheless dominated by resistance in the tissue he studied, namely Purkinje fiber. His

tracings cannot separate the resistance during depolarization from zero, so the resistance during the fast upstroke depolarization (Silvio's "spike") is certainly very low, so I imagine the same would be the case for the upstroke of other action potentials. Unfortunately, his use of Purkije fiber does not give us a clear-cut answer to all repolarizations because the Purkinje fiber action potential is broad, like that of ventricular fibers. All one say is that in the case of Purkinje fiber repolarization, the electrical resistance is less than during the action potential plateau or during the slow pacemaker current.

Student: I suppose the Purkinje pacemaker current initiates the heart beat in patients with heart block.

Professor: Yes, I am going to assume that you understand the anatomy of the conduction system of the heart, i.e., the sino-atrial cell initiates the action potential crossing the atria where they stop at the A-V insulating sheet, except at the AV node, the signal is then delayed by the bundle of His (thus ensuring contractile A-V delay). Then conduction along the Purkinje bundle branches of the endocardium to the apex and then the base, endocardium then epicardium.

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CHAPTER 4

CALCIUM AND THE HEART, PART 1

Fallacy No 4: Cardiac muscle cells do not need a cell membrane. WRONG.

This chapter brings the reader's attention to the fact that living cells are in danger all the time if the extracellular calcium concentration ([Ca^{2+}]) is higher than that within the cell. Calcium ions would flow down the concentration gradient into the intracellular muscle proteins which contract into functionless globules. This toxicity is called "calcium overload". It seems that natural selection has provided a membrane to surround the cell cytoplasm with a calcium resistant fatty double membrane (lipid bilayer). However, Ca^{2+} is required inside cells which contract, like the heart, because contraction is caused by the biochemical reaction between actomyosin contractile proteins, ATP and Ca^{2+}. For this, Ca^{2+} needs to come into the cytoplasm for contraction, and then be removed for relaxation, all without losing the Ca^{2+} overload protective function of the cell membrane. Such a system is necessarily elaborate and varies with the force of contraction required (in mammals, highest in heart and skeletal muscle which have specially ordered protein arrays = stripes or striations) to help with contractile function.

Student: Surely the cell membrane is needed to provide channels and receptors.

Professor: A more important reason is to protect the cell from calcium ions (Ca^{2+}). Intracellular calcium concentrations in cardiac muscle cells range from 10^{-7} to 10^{-5} M, i.e., the nanomolar range. The extracellular concentration of calcium is about $2x10^{-3}$, i.e., the millimolar range. Therefore, there is a huge chemical gradient for calcium to diffuse into the cell and in the absence of a cell membrane, the calcium binds to the intracellular phosphate and carbonate ions which precipitate, and the cell dies of "calcium overload". Studies of "skinned" cardiac muscle (cell membrane removed), e.g., Kentish et al. [1986] must be performed in a