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Medicine and Medical Sciences: Is there a Need for New Directions?

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Abstract

A review of recent developments revealed some important gaps in our knowledge of medicine and medical science, leading to recommendations for new directions in these subjects. Research in electrophysiology of living cells needs to focus on the electrical charge changes and electron movements. In endothelial research, measurement of changes in trans-membrane electrical potential should be measured during increases in arterial wall stress and the effect on this voltage of endothelium dependent vasodilation and nitric oxide studied. Study is recommended of the possibility of like electrical charge repulsion as a mechanism of protection of the endothelium by the endothelium-glycocalyx complex. In muscle research, study of electromagnetic forces is recommended. In clinical practice greater care is needed in the diagnosis of true hypertension and low salt diets should be abandoned for people with normal kidney function. In coronary disease, more attention should be paid to the shear stress induced activation of platelets at stenoses, and trials of blockade of this with $5HT_{2A}$ antagonists. Anti-thrombotic drugs should be administered as mg/Kg and dose titrated to each individual patient.

Keywords: *electrons, electromagnetic forces, endothelial electrophysiology, hypertension, salt, $5HT_{2A}$ receptor antagonism.*

Introduction

During my time in hospital medical practice (1960 - 2000), there were very great advances in medical diagnostic techniques and treatments. Hospital medicine was very busy and exhausting, with little time to indulge in long-term thinking, a situation which must be even more stressful today for those struggling with hospital medicine. Whilst evidence-based medicine is obviously desirable in principle, has it, by recommending treatment protocols derived from statistical analyses of large numbers of patients, created a straightjacket that inhibits concentration on the medical problems of the individual patient? All humans are different from other humans, even if they have an "identical" twin. Also, in basic life sciences, conventional theories prevail as sorts of "holy writ" which defy logic. Fresh thinking is required to allow more realistic ideas that can stimulate research that progresses both understanding of basic biological science and its application to practical medicine.

Basic Science straightjackets (two examples)

Example 1, the nature of living cells

Textbooks and courses continue to present the Nernst relation of electrolyte distribution in terms of potassium ion (K^+) concentration differences between the extracellular and intracellular compartments. However, this is not, as usually assumed, the Nernst equation [1], which is actually: Ecell = Eocell - (RT/nF)lnQ

Ecell = cell potential under non-standard conditions, i.e., during activation.

Eocell = cell potential under standard conditions, in which there is a negative trans-membrane potential, i.e., a net excess of intracellular negative charges.

R = gas constant, which is 8.31 (volt-coulomb)/(mol)

T = temperature, F = Faraday's constant, 96500 coulombs/mol. Q = reaction quotient, which is the equilibrium expression with initial concentrations rather than equilibrium concentrations.

n = number of moles of electrons exchanged in the

electrochemical reaction (mol) n is the variable, loss or gain of which in the cell mediates activation and signals function.

This the principle underlying the Bio-electric Law [2] which brings physiology into line with the principle of organic chemistry, in which the importance of electron flow from high electron density areas to lower electron density area is accepted [3].

In the case of intact living cells the high electron density sites are the mitochondria with an electrical potential of -180 to -220 milivolts (mV) [4], and the lower electron density sites include the general cytoplasm with an electric potential that varies greatly from cell type to cell type; examples are the vascular endothelial cell and cardiac ventricular cell with transmembrane potentials of approximately -80mV [5,6]. Thus, unless the mitochondrial membrane is an absolute insulater (it has, of course, a variable electrical conductance), electrons will flow at various rates from the mitochondria to the general cytoplasm to maintain the electrical negativity of the intracellular compartment. The idea that transmenbrane potentials are caused by K^+ concentration difference arises from a mathematical fit, but to back this up, one has to assume that the difference is achieved by a membrane pump, whereas it has been shown that there is not enough chemical energy for such a process [7,8]. Tied up with this false assumption is that of regarding cellular interiors as consisting of an electrolye solution, the so-called "cytosol". If so, magnetic Resonance Imaging (MRI) would be impossible. Rather, the intracellular proteins ensure that the cell contents are a gel in which the water is structured and not liquid. As proteins provide the majority of intracellular negative charges [9], K^+ ions are bound to the protein electrostatically [10], a situation that explains the high intracellular K^+ without having to invoke an energy wasting ionic pump. The overall electrical negativity of the cell interior is due to an excess of free electrons [2].

Example 2. Muscular contraction

The fixed idea in textbooks and courses is that striated muscle contraction occurs by actin thin filaments sliding between centrally fixed myosin filaments within the sarcomeres. While this is true, the dogma continues by stating that the heavy meromyosin "heads" of the individual molecules in the fibre myosin polymer, grab the thin filament to form a "cross-bridge" and pull it along like a nanomuscle! Now the thin filaments are 1 micron (micrometre, μM) in length and the working range of sarcomere length in cardiac muscle is 1.6 to 2.2μM. Therefore in the range 1.6 to 2.0 μM of sarcomere length, the actin filements from each end of the sarcomere overlap. They therefore have to re-arrange their location in the cross section [11]; how do the myosin grabbers cope with this? Further, spacing between the myosin heads along the thick filament in a single angle laterally is 43nM, different from the spacing of the active sites on the thin filament of 39nM. Herzog et al. review one of the phenomena that are not compatible with the theory that the cross-bridges attach mechanically to the thin filaments [12]. There is a situation in which mechanical binding of myosin heads to actin filaments does occur, namely in the absence of ATP. This is the rigor mortis that grows with time as the creatine phosphate and ATP deplete in the dying muscle cells. In living muscle, it seems much more realistic to postulate an electromagnetic force that draws the thin filaments towards each other. Attempts have been made [11,13]. Holohan and Marston [14] show that immobilized myosin in a motility assay can induce full bead-tailed actin filament force-velocity characteristics, when an electromagnetic field is applied in the presence of ATP. Here is an approach that ought, perhaps, to be pursued more thoroughly in future muscle research.

The main new direction proposed for future basic research is to obtain data on the changes in trans-membrane potential during changes in function of the cell. For instance, the trans-membrane potential of the vascular smooth muscle varies over a range in association with changes in tone, while the retinal cell hyperpolarises in response to photons falling upon the eye. The changes in sino-atrial and cardiac ventricular cells have been analysed [6,15]. For most cells the responses of trans-membrane potential do not seem to have been studied. e.g., endothelial cells can be depolarised by K^+ application [5] but then, so can all cells; one wants to know what happens with physiological changes in function such as increased shear stress-dependent vasodilatation induced by downstream demand for flow, and endothelium dependent vasidilators.

Pathophysiology

1. Role of the vascular glycocalyx

My main interest in this field is to try and understand the way atherothrombosis occurs in arteries [15]. The

hypothosis that glycocalyx dysfunction is the initiating factor [16] has led to many studies that are compatible with that idea [17]. The most frequently reported glycocalyx dysfunction appears to be associated with diabetes mellitus, which makes it of interest that high luminal glucose concentration inhibits shear stress-dependent vasodilation [18]. However, the mechanism by which the glycocalyx protects the endothelium from damaging adhesion molecules and cells (leukocytes and platelets) is not clear. This may be because the electrophysiology of non excitable cells has been neglected. The vascular endothelial cell has a trans-membrane electrical potential difference of about -80mV, and the glycocalyx is generally thought to be negatively charged [17], although the actual electrical potential does not seem to have been measured. Nevertheless, with the trans-membrane potential of leukocytes being of the order of -67mV and of platelets -52mV, it seems reasonable to point to a new direction for research in this area, namely electrostatic repulsion of like charges between the endothelium-glycocalyx complex and the potentially damaging blood cells [17].

2. Development of the atheromatous lesion

It is generally recognised that oxidised LDL damages glycocalyx and can lead to a lipid full plaque, characterised on coronary angiography as an eccentric lesion. Kaski [19] claims that the majority of coronary lesions are eccentric but in my West London hospital practice in the 1990s, about half were concentric on coronary angiograms. So plaque formation and rupture may not be the universal reason for angina and acute coronary syndromes. The frequency of concentric lesions recalled the illustrations of von Rokitansky [20] showing that in the cross-sectional appearance of concentric lesions, the obstructive material consisted of layers of organised thrombus. This, together with the absence of coronary disease in haemophiliacs [21], led me to propose thrombosis as a unitary hypothesis of cardiovascular risk [22] somewhat too enthusiastically, considering the obvious multiplicity of factors contributing to atherothrombosis. At least, we were pretty sure that acute coronary syndromes were caused by acute thrombosis in the coronary arteries. However, the idea that these were initiated by plaque rupture and the consequent reaction of adhesion molecules, leukocytes and platelets was unsatisfactory in explaining thrombosis within the concentric lesions. This led to a search for a factor common to both types of lesion, of which the obvious one was that the arterial lumena were stenosed. When the same flow of blood travelling along a healthy section of artery has to go through a narrower cross-section (stenosis) the blood has to speed up (convective acceleration) and this subjects the platelets to increased shear stress, causing their activation and release of serotonin. Serotonin activates more platelets through the $5HT_{2A}$ receptor, constituting a positive feedback situation (snowball effect) and thrombus growth. This process is inhibited by $5HT_{2A}$ receptor antagonists. A new direction in pathophysiology might be to pursue the haemodynamics of stenoses and their effect upon blood constituents.

We are left to find a reason for the predeliction for lesions to develop at sites of low wall shear stress within the arterial tree, which Caro [23] thought was due to increased uptake of lipid into the arterial wall at such sites, but could be due to reduced nitric oxide (NO) production which is stimulated by increased wall shear stress [17].

Clinical Medicine

1. Hypertension

One of the medical variables that is monitored most assiduously is blood pressure (BP). There are reasons to suspect that high BP is overdiagnosed, with the result that normal people are given blood pressure lowering drugs unnecessarily. One of the reasons for this is that so many measurements are made by non-doctors without consideration of the differences in arm anatomy between individuals. The standard velcro-attached cuff used in general practice can easily be too wide for a person with a short upper arm, or the cuff may be too short for a fat arm. When I started practice we had much superior cuffs that were narrow and long and could be applied to almost any arm tightly, and simply fixed by tucking in the end. Perhaps we could return to that design or measure BP at the wrist in stead? These problems are mostly overcome in in-hospital patients where good automatic machines are used by more experienced staff and the patients are settled, not seen in a clinic after waiting.

The next problem is that spot readings as recorded in general practice are sometimes used to make clinical decisions. Clearly, a patient with a high "spot" reading who has a normal average BP, recorded over 24 hours, does not have hypertension, but how often

is this investigation carried out? Further, are all the causes of hypertension looked for as thoroughly as they should? How many patients attending for "spot" measurements of BP have the possible difference in BP between the two arms, or between the arms and the legs checked? The down side for population control of hypertension is the epidemic of hyponatraaemia [24] caused by low salt diets [25]. The advocacy of low salt (Sodium Chloride, NaCl) diet today is based on false interpretions of epidemiological studies in mixed ethnic populations, which cannot be replicated in pure European Caucasian subjects [26,27,28]. More damning still, the hypothesis that developing hypertension was associated with excess salt was disproved long ago by the normality of total exchangeable sodium in such patients [29], and the failure to raise BP on administration of large quantities of salt to normal Caucasian volunteers [30]. As normal kidneys excrete any excess sodium, low salt diets should be abandoned except by those with abnormal kidney function.

2. Coronary disease

This subject has descended into confusion by a study that showed that heart stents for stable angina show no benefit over placebo [31, 32]. Perhaps a new direction would be to focus on shear-stress-induced activation of platelets and the serotonin induced positive feedback, for both acute treatment and prevention, with agents that have no effect on bleeding [33, 24, 35].

At the moment, the focus is on low fat diet and administration of statins. The latter is justified once the presence of coronary disease is established, even if the cholesterol levels are normal (which was the case in about half of our 1990s patients with acute coronary syndromes). I doubt whether it is justified in normal people, particularly those elderly who do not have the disease. Even with the disease, some elderly patients would not be motivated by the thought of an extra year of life and having to accept the side effects (as I know personally - depression and very painful muscles). As most lipids are manufacured by the body and are not directly related to the food eaten, it is difficult to justify low fat diets for the general population, for whom, "The Great Cholesterol Myth" [36] should perhaps be compulsory reading. A particular objection is decision making on the basis of total (mixed) cholesteral concentration leading to some people having the beneficial high density lipoproteins lowered by drugs. In my West London practice in the 1990's there was no correlation between total (mixed) cholesterol and prognosis, in contrast to the poorer prognosis associated with insulin resistance in non-diabetic patients [37]. Lipid lowering drugs should in my opinioin be based on LDL and $LP_{(a)}$ concentrations and whether the person has one of the hiperlipidemias with a positive family history for arterial disease. The advocacy of low fat diets might be responsible for the epidemic of obesity, often leading to type 2 diabetes mellitus. More carbohydrate seems to be eaten, possibly due to them not satifying appetite, resulting in higher calorie intake than a high fat diet (even though fat is more calorific per unit mass). Attempts are being made for people to revert from processed food to balanced fresh foods, an old tradition, but now needing to be a new direction.

3. Anti-thrombotic therapies

One of the mainstays of secondary prevention in coronary disease, venous thrombosis, pulmonary embolus and atrial fibrillation is the chronic administration of anti-thrombotic drugs. Unfortunately these drugs are not titrated to each individual patient. For instance, in the case of coronary disease, dual anti-platelet therapy is administered in fixed doses without regard for body mass, when it is obvious that they should be administered in doses notmalised for body mass, e.g., mg/Kg. Thus a small patient receiving the fixed dose is at great risk of bleeding, while a heavy patient receives little therapeutic benefit. The same consequence follows from the switch, (in patients with venous thrombosis, pulmonary embolus and atrial fibrillation) from warfarin to fixed dose anti-coagulants such as riveroxaban, with serious consequences [38]. The new direction required here is to determine the optimal blood concentration for each drug, monitor the drug concentration in the patients blood and adjust the dose accordingly. Even then, there is the problem of variable sensitivity to the drug in each patient and the effect of interactions with the other medications the patient may be receiving. In the case of arterial disease the new direction would be to switch to a $5HT_{2A}$ receptor antagonists that have no effect on haemostasis, e.g., [35].

4. Heart failure

The main change during my clinical career in the approach to chronic heart failure was the change from trying to stimulate the heart, towards protecting

the heart from sympatho-adrenergic up regulation and tackling the consequences to the periphery, leading to the use of ß-adrenergic receptor blockade and angiotensin converting enzyme inhibitors. This has undoubdedly been a success, but whatever happened to increasing ventricular contractility in heart failure? [39]. While in acute failure aortic balloon pumping seemed the most logical approach to avoid problems with adrenergic stimulation [40], in chronic heart failure, two factors mitigated against the use of positively inotropic drugs; one was that if one increased contractility by increasing calcium ion (Ca^{2+}) delivery to the contractile filaments, the increase in overall cellular Ca^{2+} caused arrhythmias and in extreme circumstances cell death from Ca^{2+} overload. The other factor was that chonic adminstration of positively inotropic drugs undoubtedly worsened long term prognosis, when the end measure was mortality. A doubtful claim was that the shortened lifespan was associated with improved quality of life. This possibility is extremely difficult to study, so it was not, even with the apparently promising combination of milrinone plus ß-adrenergic antagonism [41]. The other idea was to increase contractility by sensitising the contractile filaments to normal intracellular concentrations of Ca^{2+}, thus avoiding arrhythmias [42], but this also was not followed up. Is that a pity? We do not know, but the principle of accepting a worse life-span in order to increase the quality of life during that shorter life span would seem to me to be a worthy objective in the elderly, from a philosophical if not a practical research point of view.

Conclusions

Recent concerns of mine that I have expressed elsewhere should, if thought to be worthwhile, lead to new directions in internal medicine and its supportive sciences:

1. A research focus on the electrophysiology of living cells other than neoron and muscles.
2. In muscle, more research on electromagnetic forces.
3. In endothelial research, measurement of changes in trans-membrane electrical potential during increase in arterial wall stress and the effect on this voltage of endothelium dependent vasodilators and nitric oxide.
4. Study of the possibility of like electrical charge repulsion as a mechanism of protection of the endothelium by the endothelium-glycocalyx complex.
5. Greater care in the diagnosis of true hypertension.
6. Abandonment of low salt diets for people with normal kidney function.
7. In coronary disease, more attention to the shear stress induced activation of platelets at stenoses, and trials of blockade of this with $5HT_{2A}$ antagonists
8. Anti-thrombotic drugs to be administered as mg/Kg and dose titrated to each individual patient.
9. In elderly patients with chronic heart failure, a search for more objective ways of assessing quality of life other than mere questionaires.
10. Encourage a mixed diet of fresh produce and discourage processed food.

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