INTRODUCTION TO MEDICAL PHYSIOLOGY:
CELLULAR MEMBRANES AND TRANSMEMBRANE TRANSPORT
OF SOLUTES AND WATER

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This article summarizes the comments made in the introductory session of the
Medical Physiology course taught at the University of Alabama School of
Medicine. The main thesis is that learning physiology is easier when fundamental
principles are first delineated. Four general principles of physiology (mass balance,
force-flow, capacitance, and equilibrium) are discussed. Clinical medicine becomes more
comprehensible when these basic principles are understood. Cellular Physiology is
taught first because it forms the conceptual basis for what follows in the course. The idea
that the root of clinical medicine lies in the basic sciences is emphasized.


Key words: equilibrium; mass balance; capacitance; diffusion

Despite the revision of many medical school curricula
toward more problem-based learning, computer-
based instruction, and small group conferences, many
schools still rely primarily on the lecture format of
instruction for the basic sciences. More often than
not, the introductory sessions in a systems medical
physiology course begin with the topic of cellular
physiology, specifically membrane transport phenom-
ena. Moreover, the introductory remarks made by the
instructor effectively set the tone for the remainder of
the course. For physiology, it is imperative that
students understand the integrative nature of the
discipline as well as become aware of the fact that
physiology is not a static science, but that many
important discoveries still remain to be made (2, 24).
To this end, I would like to summarize for you the
comments that are made to the first year medical class
at the University of Alabama School of Medicine in the
hope that this approach may be useful to those
charged with providing an overview of physiology at
other schools. The first ten lectures of the course deal
with the topic of cell membranes and transport, but
the emphasis is on the importance of an integrated
approach and how this subject matter, although
conceptually difficult and theoretical, nonetheless will
be used throughout the remaining sections of the
course. Table 1 summarizes the nine areas of physiol-
ogy that are covered in the course. Cellular Physiology
is taught first because it, in essence, forms the basis for
what is to follow. In fact, a more limited view of the
cell is taken, and the focus is on the plasma membrane
and the mechanisms by which solutes and ions
traverse this organelle.

Why do we follow this approach? The relevance to
medical practice becomes obvious from a small sam-
ping of recent literature in which specific human
disease states have been clearly attributed to transport-
related deficiencies. Table 2 summarizes some of
these transport-related diseases with respect to each
of the systems of physiology that are studied. Many of
these diseases are genetically based (e.g., malignant
hyperthermia, hyperkalencic periodic paralysis, para-
myotonia congenita, Liddle's disease), whereas others
are not [e.g., acquired immune deficiency syndrome (AIDS) dementia complex, cholera]. If the physiological basis of clinically relevant diseases is discussed at the very beginning of the course, the ideas and the importance of physiology as a subject that is essential for medical practice as well as an area ripe for further scientific investigation are firmly established. In addition, three other examples are taken from the literature that show very distinct involvement of ion transport processes in physiological recognition systems (Table 3). First, recent papers show that there are oxygen-sensitive K⁺ channels located in the plasma membrane of Type I glomus cells in arterial chemoreceptors in the carotid body (13, 25). Second, the recent cloning of a Ca²⁺-sensing receptor in the parathyroid gland and the potential coupling mechanism that is involved in parathyroid hormone release are discussed (6, 19). Third, an example of L-type Ca²⁺ channels being localized to branch points in arterial resistance vessels is presented (15). Of course, any other relevant examples can be used. It is advantageous to include such examples to reemphasize the necessity and importance of understanding the basic transport-related material and to establish further the contention that transport phenomena span all aspects of physiology.

The objectives of these introductory lectures are listed in Table 4. At the end of this series of lectures, an entire period or two is dedicated to an in-depth discussion of a specific ion transport-related disease, from the clinic to the laboratory. In recent years we have alternated between cystic fibrosis, AIDS dementia complex, and Liddle’s disease as clinical correlation topics. This discussion serves several functions: it introduces students to specific clinical symptoms associated with a given disease, it provides a convenient forum within which to merge physiological principles with the clinical manifestations of the disease, and it translates the theory of the classroom to real-life situations. Oftentimes the services of a clinician are employed, and actual patients are presented. Again, this approach reemphasizes the strong interactions and intellectual ties between basic physiological science and medical practice. Furthermore, it clearly

### TABLE 1

**UASOM medical physiology**

- Cell Physiology
- Neurophysiology
- Muscle Physiology
- Cardiovascular Physiology
- Respiratory Physiology
- Renal Physiology
- Gastrointestinal Physiology
- Endocrine Physiology
- Fetal Physiology

UASOM, University of Alabama School of Medicine.

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TABLE 3
Examples of ion transport system involvement in physiological recognition

| Arterial chemoreceptor O₂ tension detection by carotid body O₂-sensitive K⁺ channels in plasma membrane of type 1 glomus cells (12, 24) |
| PTH release (6, 18) |
| 120 kDa Ca²⁺-sensing receptor |
| Vasoconstriction of renal resistance vessels |
| L-type Ca²⁺ channels at arterial branch points (14) |

PTH, parathyroid hormone. Reference nos. in parentheses.

TABLE 4
Cellular physiology: objectives

1) Understand and use four basic principles of physiology.
2) Distinguish the concepts of equilibrium and steady state.
3) Understand the construction and function of biological membranes.
4) Comprehend and be able to solve problems related to non-electrolyte and electrolyte diffusion.
5) Differentiate between different models of transport (e.g., exchangers, cotransporters, carriers, channels).
6) Recognize and analyze ion channels.
7) Understand biological potentials, especially resting membrane potentials.
8) Apply and use above knowledge in clinically important situations.

FOUR IMPORTANT PRINCIPLES OF PHYSIOLOGY

I contend that there are four major physiological concepts that, in essence, link all of the systems presented within a general medical physiology course. I maintain that, if these concepts, embodied in specific equations, are understood, the students’ grasp of physiology will be better. These same concepts recur, not only in the cellular physiology section, but in the muscle, cardiovascular, respiration, gastrointestinal, and renal sections of the course. The concepts can be obscured within the context of the terminology, but they are nonetheless present.

The first of these general concepts is conservation of mass: matter cannot be created nor destroyed. This is also known as the mass balance principle, and it is embodied in a very simple equation

\[ C_1V_1 - C_2V_2 \]

where C is concentration of any substance (in amount/volume) under initial (1) and final (2) conditions, and V is volume under initial (1) and final (2) conditions.

For example, if 1 ml of a 1 M solution of NaCl is added to 99 ml of pure water, the final concentration of NaCl can be calculated to be 0.01 M. Another application of the principle of mass balance can be demonstrated from circulation, considering O₂ delivery and egress from a muscle capillary bed. The example can be simplified as indicated in Fig. 1. Assume, for instance, that the concentration of arterial oxygen (Cao₂) is 10 mM, the cardiac output (CO) is 5 l/min, and the oxygen consumption (VO₂) of the muscle is 10 mmol O₂/min. The question becomes: what is the concentration of oxygen in venous blood (Cvo₂)? At this point, the concept of steady state needs to be introduced. Steady state can be defined as a condition in which a system, or a given property of a system, is constant in time. Therefore, with the application of the mass balance principle in conjunction with the steady-state assumption, it becomes apparent that the total amount of oxygen going into the system must be equivalent to that going out.

Total input amount of O₂/min

\[- \text{Total output amount of O₂/min} \]

Of course, there are two output conduits, namely, the amount of O₂ being consumed by the muscle (VO₂) per unit time and the amount of O₂ flowing out through the venous system per unit time (Cvo₂·CO). Thus

\[ (C_{\text{a}})CO = V_{\text{O₂}}(C_{\text{v}}) \]

This equation is often referred to as the Fick principle. Therefore, by solving this equation for Cvo₂, the arterial content of the venous blood is calculated to be 8 mM.

The second major principle of physiology is the so-called force-flow relationship. An important attribute of the living condition is movement. We can walk, we can move our limbs via contraction of our
FIG. 1. Schematic representation of blood flow through a muscle bed. $C_{aO2}$ and $C_{vO2}$, arterial and venous concentrations of oxygen (in ml/ml), respectively; $V_{O2}$, oxygen consumption (in ml/min).

So, when discussing membrane voltages driving ion movement, implicit in such a statement is the fact that the voltage drop occurs across a finite distance, i.e., the membrane. This force-flow relationship is seen over and over again throughout physiology. It is used in discussions of solute flow, the flow of blood, the flow of gas, the flow of metabolic substrates, etc. These flows, in general, have a good deal in common. They are comprised of small molecules in solution whose movements are regulated by the permeability properties of biological membranes.

The third important concept of physiology is that of capacitance. Capacitance can be defined as the amount or volume of matter a system is able to accommodate under a given set of conditions. When we inhale and exhale, we are filling or emptying our lungs with gases. The lungs have “capacity”; if a subject inhales maximally, his or her lungs cannot accommodate any more inspired air. The lungs are then said to be at their maximal inspiratory capacity. Likewise, the veins are considered capacitance vessels and are under strict autonomic nervous system control. Blood can therefore be mobilized from or stored within the venous system as the physiological needs of the organism demand. For example, in arterial hypotension (as occurs during severe hemorrhage), the smooth muscle surrounding the venous capacitance vessels con-
stricts, thus shifting blood volume to the arterial side to maintain or restore arterial pressure. Another electrical analogy of the concept of capacitance is that of the parallel plate capacitor. The amount of charge \( q \) that can be stored in such device is equal to its capacitance \( C \) times the imposed voltage \( V \)

\[
q = CV
\]

As indicated above, the concept of capacitance will be applied when one considers the volume of air in the lungs or the amount of blood stored in the veins. Thus the amount or volume of a system is equal to the capacitance of the system multiplied by the pressure exerted \( P \)

\[
\Delta V = C \times P
\]

Figure 2 shows the general relationship between volume and pressure in a capacitance organ such as the lung or a blood vessel. From such a relationship, it can be seen that the slope at any point on the curve is equal to the capacitance (i.e., \( C = dV/dP \)). Therefore, the capacitance of most expandable systems is not constant, but rather is state dependent. What this graph shows is that the volume-pressure curves are non-linear; they arc sigmoidal in shape. At low pressures, the capacitance is very small, that is, the system can change its volume by a given amount only with a very large change in pressure. At intermediate pressures, the capacitance increases. At very high pressures, the capacitance is again decreased. A useful example demonstrating this variability in capacitance with volume is what happens when one inflates a balloon. At first, it is very difficult to expand a balloon (it takes a large pressure change to alter the volume of the balloon slightly; i.e., at low pressures, there is a small capacitance). Once the balloon begins to expand, it becomes relatively easy to inflate (higher capacitance range). Then, finally, at very large volumes (where the capacitance decreases), it will again take a relatively large pressure change to produce a small increase in the balloon's volume. The capacitance of a rigid vessel (like a lead pipe) is zero: the volume (assuming an incompressible material) is independent of applied pressure.

The fourth important concept of physiology is that of thermodynamic equilibrium. Equilibrium is the condition at which the free energy change of a system or a component of a system is zero, i.e., when all driving forces (inherent or imposed) that act on that system are equal in magnitude and opposite in direction. For non-charged molecules, equilibrium is obtained when the concentration is equal at every point in the system. For ions, thermodynamic (electrochemical) equilibrium \( E_i \) is defined by the so-called Nernst equation

\[
E_i = \frac{(RT/zF)}{26 \text{ mV}} \ln \left( \frac{[\text{ion}]_{\text{out}}}{[\text{ion}]_{\text{in}}} \right)
\]

where \( R \) is the gas constant, \( T \) is the temperature (in degrees Kelvin), \( z \) is the valence, and \( F \) is the Faraday constant. At 37°C, \( RT/F \) equals 26 mV. This equation is used repeatedly in calculations of driving forces for ion movements, as a criterion to decide whether an ion is actively or passively transported, as a basis for understanding the action potential and other excitable membrane phenomena, etc.

Another equation that directly relates to the concept of equilibrium is the Henderson-Hasselbalch equation. This equation is really a statement of chemical equilibrium. Consider aspirin for instance. Aspirin is a weak acid, that is, it exists in two forms: protonated (uncharged) or unprotonated (charged). We can write

\[
HA \rightleftharpoons A^- + H^+
\]

where \( K_{eq} \) is the equilibrium dissociation constant.
Taking logarithms of both sides of this equation

\[ \log K_{eq} = \log H^+ + \log \left[ A^- \right]/[HA] \]

and

\[ -\log K_{eq} = -\log H^+ - \log \left[ A^- \right]/[HA] \]

Remember, pH is defined as \(-\log H^+\), and \(pK_a\) is \(-\log K_{eq}\). Therefore,

\[ pK = pH - \log \left[ A^- \right]/[HA] \]

or

\[ pH = pK_a + \log \left[ A^- \right]/[HA] \]

Many other clinically important compounds, for example, the local anesthetic procaine, need to be ionized for pharmacological activity. In addition, many of these compounds, such as procaine, are most effective from the cytoplasmic side of the nerve membrane. Yet it is the ionized form that most readily penetrates the nerve fiber. Thus acidic pH in tissue, such as occurs in inflammation, would result in a dominance of the charged form of the drug and poor penetration. Alkalization would, therefore, increase the effectiveness of the anesthetic.

**CONCLUSION**

It is important to emphasize that physiology is the study of all aspects of function, of how things work and how they are regulated, and thus cell physiology is the study of cellular function. From a biased, but I think correct, perspective, I try to impart the idea that the student should come away from the Cell Physiology section of the course with the appreciation that the study of function (i.e., physiology) is related to the study of membrane transport phenomena; function and transport are intimately associated with each other. More generally, compartmentalization and transport between compartments are the essence of physiology. For example, take the mitochondrion, the energy factory, or, as H. Davson (9) put it, the powerhouse of the cell. For the mitochondrion to produce ATP efficiently, it must couple oxidation to phosphorylation. For this coupling to occur, there must be a very steep electrochemical potential energy gradient for hydrogen ions across the inner-mitochondrial membrane. If this gradient is in any manner dissipated, e.g., by an uncoupler of oxidative phosphorylation such as dinitrophenol or gossypol (a male contraceptive agent), energy production ceases and cell function, including protein synthesis, cell volume regulation, etc., is severely and, in some cases, irreversibly compromised.

It is important to emphasize that cellular physiology is not any more fundamental than organ physiology in terms of understanding how entire organisms function. If one really wants to appreciate and comprehend how the kidney concentrates urine, for example, a complete knowledge of the physiology and transport capabilities of each and every renal cell is pointless without knowing how the cells are assembled and interact within the kidney itself. The same is true for any other organ system.

The cell membrane subserves an irreducible role in the life cycle of a cell. Indeed, life undoubtedly would not have evolved were it not for the existence of the plasma membrane (26). Although a membrane confines essential macromolecules within specified compartments and effectively insulates a cell from its surroundings, the cell must be able to recognize specific signals, sense its immediate microenvironment, and respond appropriately to a myriad of physiological and biochemical inputs. Invariably and universally, signal transduction, information transfer, and mechanical effectors are mediated at some stage by ion movements across cellular membranes. The depth of involvement of these transport events in important physiological processes has not yet even begun to be appreciated, let alone understood. A disruption of the structural or functional integrity of the membrane or its constituent transport components can have dire clinical consequences. Referring to the disease of cystic fibrosis, it is almost staggering to realize that only one amino acid deletion in a single transport protein containing 1,480 total amino acids (an error of only 0.07%) can lead to pancreatic enzyme insufficiency, chronic lung infections, pulmonary hypertension, bronchiectasis, and right ventricular hypertrophy, and limit the life span of such an affected individual to some 30-odd years (12). The scope and influence of membrane transport systems extend to metabolic processes such as protein synthesis and DNA replication, ATP production, nerve conduction, muscle contraction, volume regulation, fertilization,
growth and differentiation, hormone secretion and transduction, and the production of specific secretions and adsorbrates by epithelial tissues, just to name a few. It should be apparent, therefore, that the scope of physiology encompasses just about any process you can think of, and, most importantly, the essence of cell physiology is the membrane. I would like to conclude by quoting E. N. Harvey, who wrote in the forward to H. Davson and J. F. Danielli’s classic monograph The Permeability of Natural Membranes (10) in 1952.

Just as chemistry could not have developed without test tubes to hold reacting substances, so organisms could not have evolved without relatively impermeable membranes to surround the cell constituents. This barrier between the inside and the outside, the inner and external world of each living unit, has been and always must be considered one of the fundamental structures of a cell. No one can fail to be impressed with the great difference in properties of living and dead cells. The dead are completely impermeable to diffusible substances while the living retain one material and pass another. This difference, selective permeability, is so marked that it becomes the surest test to distinguish the living from the dead, holding where all other methods fail. It can truly be said of living cells, that by their membranes ye shall know them.

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