Electrochemical field effects in biological materials: electro-osmotic dewatering of cancerous tissue as the mechanistic proposal for the electrochemical treatment of tumors

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Some recent excellent papers on the electrochemical treatment (ECT) of tumors provide observations for an analysis of this phenomenon from an electrochemical point of view. An attempt is made here to develop the idea that ECT is a case of electro-osmotic dewatering (EOD) of the tumor material with the consequent changes in pH, with the concomitant role of reactions at the electrodes. Some quantitative considerations explaining the role of electrochemical double layers, zeta potential and associated quantities during the electro-osmotic process are outlined. A capsule summary of the factors that may be involved in necrosis of the tumor tissue is given in which the electro-osmotic dewatering at the anode and excess water accumulation at the cathode are the paramount effects, together with the associated pH changes.

1. Introduction

Following the pioneering studies of Nordenström on the electrochemical treatment (ECT) of cancerous tumors [1–5], a very extensive program of this type of treatment has been successfully carried out in China and recently reported [6–9]. These splendid studies have put forward a very convincing case for the efficacy of the electrochemical treatment for tumors.

The wealth of experimental data reported in the foregoing studies provides an opportunity for an electrochemist such as the present author to explore this work in terms of modern electrochemical theory [10–15] with a view to provide a quantitative description of the electrochemical mechanisms that may be involved: hence the present communication. In particular, an attempt will be made to indicate the manner in which the efficiency of the electrochemical treatment might be increased in terms of the desired goal of the annihilation of tumors. Elementary descriptions of tumors needed to follow the arguments presented here are available [1, 16, 17].

It is the first time that electrochemical treatment has been successfully used on such a vast scale [6–9] in a surgical fashion; it is most desirable, therefore, to provide some theoretical foundations to this technique in terms of electrochemical effects and changes that would be expected to operate during ECT of living biological material comprising the cancerous tissue.

2. Summary of salient experimental observations

In a *typical* tumor ECT, a direct current (d.c.) voltage of 8.5 V is applied between two platinum electrodes inserted 3 cm apart in a cancerous tissue (e.g. liver tumor), causing a flow of 30 mA electrolysis current; this current is made to flow continuously for 69 min giving the passage of total charge of 124 C [7]. More generally, voltages of about 6–10 V with currents of 40–100 mA are applied to platinum electrodes embedded in the tumor from 1–3 cm apart, with electrolysis being carried out for 1–2 h with the passage of charge being in the neighborhood of 100–200 C [9]. The main observations are as follows:

1. Water migrates from the anode to the cathode.
2. The anodic ''site'' in the tissue becomes strongly acidic and the cathodic site strongly alkaline.
3. Higher concentrations of Na^+ and K^+ in the tissue around the cathode (which has also become strongly alkaline) are observed; not much change in the concentration of multivalent cations such as Ca^{2+}, Mg^{2+}, Mn^{2+}, Cu^{2+} and Al^{3+} occurred during the ECT.
4. The denaturation of protein was caused by the ECT; haemoglobin is converted to acid haemin around the anode and alkaline haemin around the cathode.
5. Chlorine and hydrogen evolution are observed at the anode and cathode, respectively; chlorine causes, not

unexpectedly, some bleaching of the local tissue whereas hydrogen produced local cavitation.

6. The cell metabolism and its existing environment are disturbed severely by the electrochemical treatment, causing the destruction of both normal and tumor cells rapidly and completely.

Although a number of reactions and events, that may contribute to the destruction of tissue, take place during the ECT treatment, it seems that water transport from the anode to cathode is the *fundamental* event, together with acidity changes associated with the electrode reactions at the anode and the cathode. For example, it has been stated [1] that...''electro-osmosis plays an important role in the transport of water in the tissue. In this mechanism a BCEC (defined by Nordenström as ''biologically closed electrical circuit'') is a *pre-requisite*, as are narrow interstitial channels lined with fixed charges''. Nordenström again states [1]: ''The destroyed and intermediate zones also are dehydrated, due to electro-osmosis''.

We wish to pursue this line of thinking further in this paper. In particular, we wish to present a model and some quantitative considerations that delineate Nordenström's idea of electro-osmosis [1] through the narrow interstitial channels lined with fixed charges as the mechanism of the electrochemical destruction of the tumor tissue. The role of electrode reactions and other events as possible contributory factors will also be examined. And, finally, an attempt will be made to provide some clues which may further enhance the efficacy of the ECT treatment.

3. Model of electro-osmotic dehydration of tissue and reactions at electrodes

A schematic of a solid tumor is presented in Fig. 1 and an exploded detail of the small portion of Fig. 1 is shown in Fig. 2 [17]. Note the tumor cells floating in the extracellular medium called the interstitium (Fig. 2). Now we observe that the net charge on the cells of mammals is negative [1, 18]; this negative surface charge

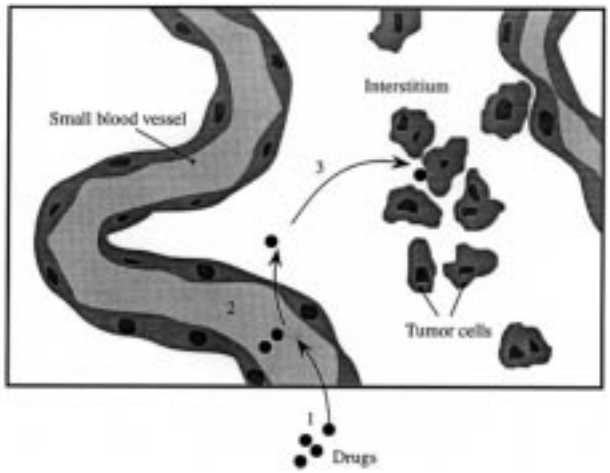


Figure 2 A detailed depiction of a tiny section (• in Fig. 1) of this tumor, showing tumor cells, interstitium, a small blood vessel and the route that a drug in the chemotherapeutic treatment takes. Adapted from Jain [17].

must be balanced by the positive charge in the extracellular fluid at the cell membrane–interstitium interface to form a so-called electrochemical double layer [18], as arises from the electrostatic requirement of electrical neutrality at the interface. One thus arrives at a schematic description of negatively charged tumor (cancerous or normal) cells floating in the extracellular fluid creating surface electrical double layers and with, between the cells, narrow intercellular fluid channels in the interstitium (Fig. 3). When a d.c. current is passed between the two electrodes embedded in the tumor, electro-osmotic flow of water occurs from the anode to the cathode, as described below.

The basic point here is that ECT causes a net flow of water from the anode to the cathode, causing electro-osmotic dewatering (EOD) of the tissue.

The EOD is based on the electrically-induced flow (namely electro-osmosis) of water trapped between the tumor cells (Fig. 3). Such electrically induced flow is possible because of the presence of electrochemical

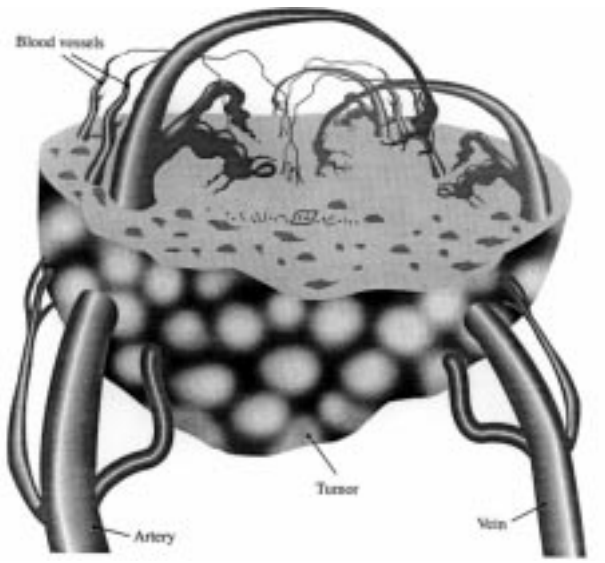


Figure 1 Idealized solid tumor, after Jain [17]. It has been partly cut away to reveal the complex network of blood vessels.

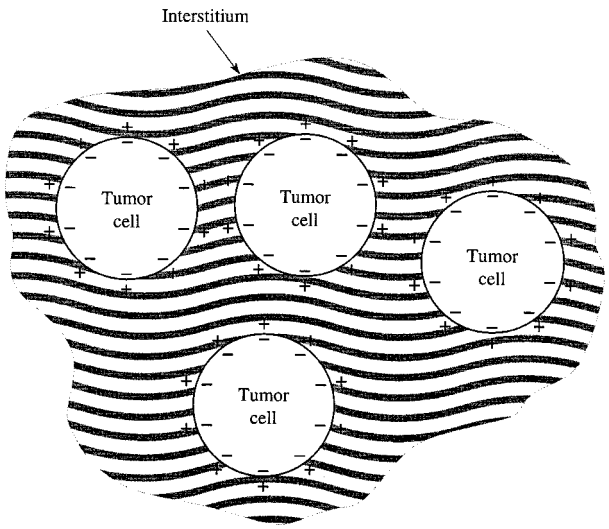


Figure 3 A schematic of tumor cells with extracellular fluid from the interstitium trapped between them. The electrochemical double layer is indicated for each negatively charged tumor cell with positive ions (in water) poised against the negative charge.

double layer at the cell–interstitium interface; in this double layer (Fig. 3), the charges on the cell surface are electrically balanced by the opposite charges in the interstitium, which is actually an electrolyte because of the presence of some salts, hydronium or hydroxyl ions etc. The structure and potential gradients of such a double layer are shown in Fig. 4, by analogy with a metal–electrolyte interface [19].

In this situation, the tumor cells are the immobile phase and the electro-osmotic flow causes the water to move as a ''plug'', the entire velocity gradient being concentrated at the cell surface in a layer of the same order of thickness as the diffuse double layer (Fig. 4). In concentrated solutions, the thickness of the diffuse double layer is quite small (< 1 nm) whereas in very dilute solutions (as are indeed represented by the water interstitium), the diffuse double layer can assume much larger values ($\sim 10^2$–10^3 nm) depending on the concentration of ions in the water. The electro-osmotic movement of water between the tumor cells is exactly similar to the electro-osmotic flow in a capillary pore (Fig. 5): the thin layer of charged fluid (i.e. water containing some ions) next to the cell wall moves like a ''single ion'' (hence the analogy of a ''plug''), under the action of the electric field in a direction parallel to it [20]. The origin of the electrochemical double layer arises from the requirements of charge neutrality in which the surface charge on the cell surface must be balanced against the opposite charge in the water (or any other fluid in a more general case).

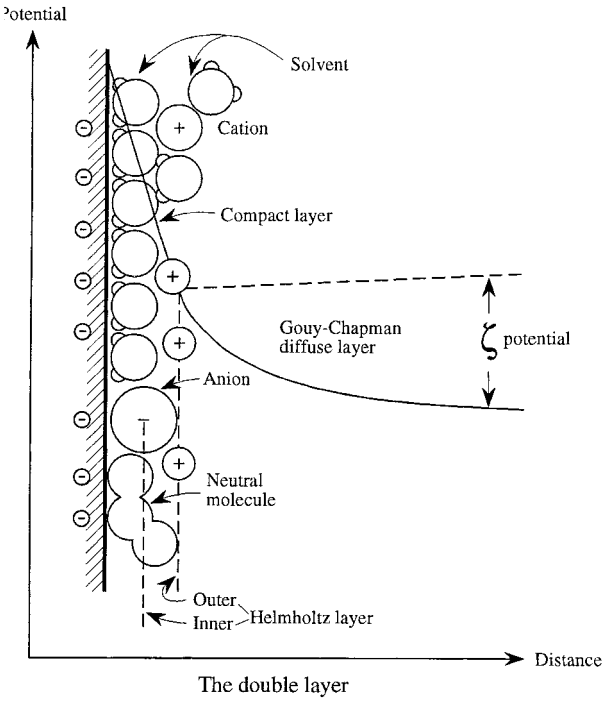


Figure 4 A small portion of the electrochemical double layer at the tumor cell–extracellular fluid (electrolyte) interface is shown to depict the microscopic structure and the potential drops involved, by analogy with the metal–electrolyte interface; taken from Conway [19].

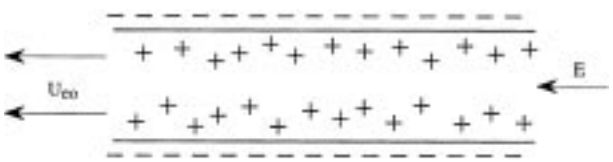


Figure 5 A schematic of the electro-osmotic flow of the medium (e.g. an electrolyte) in a capillary caused by the flow of counter ions as a ''plug'', under the influence of the applied electric field, E : U_{eo} is the convective liquid velocity from electro-osmosis. Adapted from Everett [20].

Quantitatively, the convective liquid velocity from electro-osmosis, U_{eo}, is given by the Helmholtz–Smoluchowski relation [14, 15]

$$U_{eo} = \frac{\varepsilon \zeta E}{\mu} \tag{1}$$

where ε is the permittivity of the extracellular solution; μ is the viscosity of the extracellular solution; ζ is the so-called zeta potential of the cell surface (see Fig. 4); E is the applied electric strength, defined as the minus of the gradient of the electrical potential (see Fig. 5).

The ζ potential is the potential difference between the plane of shear (or slipping plane) and the bulk solution. From Equation 1, it is clear that for a given situation of water (electrolyte) in the interstitium, the U_{eo} is proportional to the zeta potential and to the applied field strength. Also in a real situation of EOD, it is necessary to use the so-called ''length-averaged value'' of the zeta potential in order to take into account the effect of the axially variable zeta potential on the electro-osmotic velocity.

Further, since both the zeta potential and the electric field depend on the ionic concentration and pH of the fluid (water in our case), the variations in electro-osmotic velocity can be expected as the dewatering experiment progresses in time.

It should be noted from Equation 1 that for the EOD to occur, the passage of electric *current* is not required, if *ideally* one could develop high E (V cm^{-1}) without the passage of significant electrical current. However, in practice, the cell–interstitium medium has a given resistance R so that

$$i = \frac{V}{R} = \frac{E}{R} \qquad \text{(for tumor thickness} = 1\,\text{cm)} \tag{2}$$

It is the passage of this *current* that causes the electrochemical reactions at the two electrodes inserted in the tissue for applying the potential gradient (i.e. field) necessary for the electro-osmotic flow to occur. The electrode reactions at the anode and cathode induced by the passage of this current result in a number of effects, e.g. changes in pH near the electrodes which give rise to concentration gradients in the bulk of the tumor causing changes in ζ values near the electrodes which result in reduced electro-osmotic flow, as the ECT proceeds in time.

We note that before the ECT, the initial pH of the tissue (more particularly for us, of the extra-cellular fluid) is around 7, i.e. neutral or nearly neutral. When the d.c. power is on during the ECT, there are the usual electrolysis events giving the evolution of H_2 at the cathode and $O_2 + Cl_2$ (depending on the single electrode potential of the anode, the proportion of O_2 and Cl_2 will change; the anodic potential in turn depends on the parameters of electrolysis) at the anode, as follows

$$\text{Cathode: } 2H_2O + 2e \rightarrow H_2 + 2OH^- \quad (3)$$

$$\text{Anode: } 2H_2O \rightarrow O_2 + 4H^+ + 4e \quad (4)$$

and/or

$$\text{Anode: } 2Cl^- \rightarrow Cl_2 + 2e \quad (4a)$$

The evolution of hydrogen at the cathode leads to the build-up of alkalinity; the evolution of oxygen at the anode causes an increase in acidity because the protons generated by Equation 4 immediately undergo hydration to yield H_3O^+ entities. This is indeed experimentally observed. The chlorine evolution reaction (Equation 4a) is merely concomitant to the evolution of oxygen.

It is important to emphasize here that during electro-osmosis, the water flow is *always* from anode to cathode, as indicated in the schematic in Fig. 6. This arises from the electrostatics of the situation in which the water velocity profile follows the direction of the electric field, i.e. from the positive electrode (anode) to the negative electrode (cathode), as depicted in Fig. 7.

Thus the foregoing analysis clarifies the two main observations of ECT, namely, the dehydration and acidity at the anode, and, excess hydration and alkalinity at the cathode. It will also explain the relative higher concentrations or Na^+ and K^+ at the cathode since Cl^- ions must have migrated to the anode and gotten discharged there, leaving a relative excess of Na^+ and K^+ in the vicinity of the cathode at the end of the ECT.

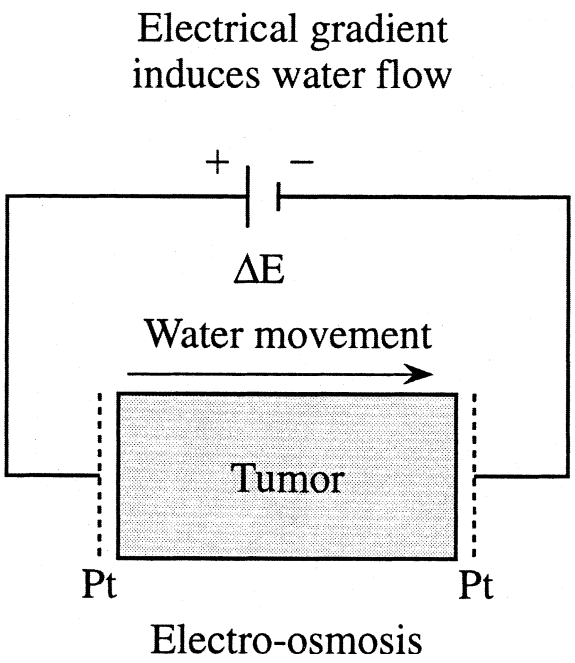


Figure 6 A schematic of the electro-osmotic experiment during ECT of a tumor.

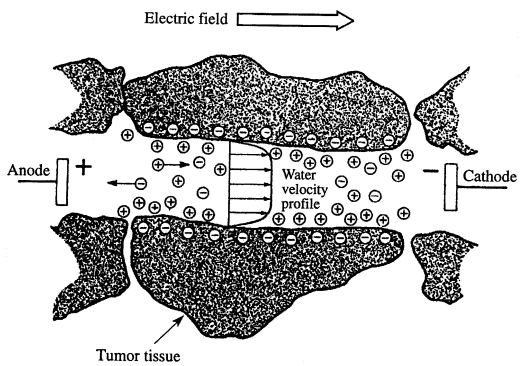
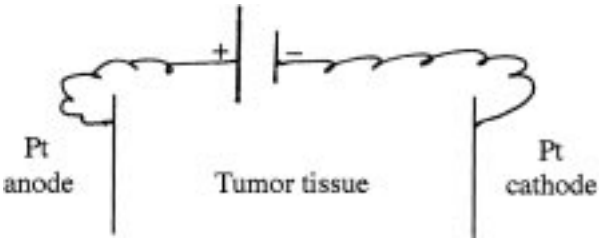


Figure 7 Electro-osmosis depicted in the negatively charged tumor tissue wall enclosing an interstitial channel carrying extracellular liquid; the water movement follows the direction of the field, i.e. always from the anode to the cathode.

4. Components of voltage applied to a platinum–tumor tissue–platinum configuration during ECT

Consider the electrochemical system involved in the ECT as



The total applied voltage, V, in this system is constituted by various components and can be written as

$$V = E^0_{H_2/O_2} + \eta_{anode} + \eta_{cathode} + IR + \frac{RT}{F}\,\text{pH} \quad (5)$$

where $E^o_{H_2/O_2}$ is the reversible potential between the hydrogen and oxygen electrode ($= 1.23$ V) or between the hydrogen and the chlorine electrode ($= 1.36$ V); η_{anode} is the anodic overpotential during ECT and its minimum expected value will be ~ 0.3 V, for conditions of detectable oxygen evolution; $\eta_{cathode}$ is the cathodic overpotential during ECT and its minimum expected value will be ~ 0.1 V, for conditions of detectable hydrogen evolution; IR is the resistive drop in the tumor (note: its value during open circuit measurement with a high-input impedance voltmeter will be 0 V; however, during electrolysis involving the passage of high currents, IR would become significant, e.g. $\sim$ 1–10 V); $\frac{RT}{F}$pH is the voltage drop between the anode and the cathode due to the pH gradient in the tumor; at the end of ECT, it can change upto 10 pH units (i.e. 0.590 V); R is the gas constant, F is the Faraday and T is the temperature in degrees Kelvin.

Thus at the beginning of ECT with minimal current ($\sim$ 1 mA) and uniform pH (neutral) between the anode and the cathode, the required voltage can be as low as 2.5–3 V. Towards the end of ECT (high pH gradient, dry anode–tissue interface and thence high IR), especially with a high current ($\sim$ 100 mA) and thence high η_{anode} and $\eta_{cathode}$ values, the required voltage could begin approaching 15 to 20 V.

5. Factors in necrosis caused by ECT

The most important factor in tissue death during ECT appears to be dehydration in the anode area and excess hydration (oedema) in the cathode area. This factor is reinforced by high acidity at the anode and excess alkalinity at the cathode. Hyperthermia would appear to be a minor factor and important only towards the end of ECT experiment when the anode area is quite dry and

thence of high electrical resistance and supports enhanced local heating.

Oxidation by Cl_2 (or chloride radicals adsorbed at the platinum electrode as Pt–Cl), O_2, O_3 (which must be evolved in traces at the high anodic potentials attained in ECT carried out at high current densities) and oxygenated radical species adsorbed at the anode are no doubt responsible for necrosis in the tissue around the anode; one can even see visible changes such as bleaching and/or other color changes. Around the cathode, the erosive damage may be caused by the profusely evolving hydrogen. Also, hydrogen evolution would expel any oxygen in the tissue around the cathode so that ''respiration'' by the tumor cells needed for their survival and growth would be inhibited, leading to their necrosis.

The ''traumatic'' changes brought by ECT might tend to break and dismantle the hydrogen-bonding network of DNA of the tissue thus suggesting another mechanism for necrosis; coagulation necrosis at or around the electrodes has also been observed. Most of these factors have been recognized by the workers in this field, in particular by Nordenström [1, 2] and are being mentioned here only as a recapitulation.

6. Possible improvements in the electrochemical treatment of tumors

If one accepts the notion that necrosis results principally from the EOD and the associated pH changes brought about by the ECT treatment, one can propose some possible avenues to improve the process.

By drawing analogy from the case of EOD of electrolyte trapped in the insterstices between fine clay particles (cf. Fig. 3 in which tumor cells are replaced by negatively-charged fine clay particles), one notes that electrode reactions at the anode and cathode cause pH changes that reduce the rate of water removal as the ECT proceeds; in other words the initial ζ potential (cf. Equation 1) assumes lower values with time (due to pH changes) as the ECT proceeds. In order to restore the original ζ potential value, one should gradually lower and then stop the current and short-circuit (after disconnecting the power source) the anode and cathode for a couple of minutes before restarting the ECT; this short-circuiting restores the original ζ potential and thence the high rates of dewatering observed at the commencement of the process [14, 15]. Also, subsequent to the short-circuiting, a *reversal* of the direction of the current for a minute or so also achieves the same goal in a more enhanced manner [14, 15]; this latter would then correspond to the Phase II of ECT in the terminology of Nordenström [5] in which a reversal of the current in the tissues is achieved. In electrochemical terms, this restores the high ζ potential (Equation 1 here) and therefore causes the recommencement of EOD at high rates once the normal polarity of the ECT is re-established. Alternatively, the original value of the zeta potential may be restored by infusing an alkaline saline solution to the anode by means of electrode systems described by Nordenström [1].

7. Conclusions

1. The analysis of the ECT from an electrochemical point of view shows that this process is a case of EOD of the tumor tissue, as has been qualitatively suggested by Nordenström [1] and others previously.

2. The EOD picture presented here explains all the main experimental observations, e.g. dehydration near the anode and oedema near the cathode, as well as the experimentally found pH changes and other factors believed to be involved in necrosis.

3. The analysis provided also makes connection with the notion of Phase I and Phase II in ECT put forward by Nordenström [5].

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