later the tumorous tissue[8]. Our answer is that the particles are capable of combining with membranes to the extent of forming a localized abnormal matrix. Depending on the degree of aqueous matrix distortion, the result can vary from nerve tissue irritation to neoplastic induction.

This abnormal matrix can expand by any of a number of mechanisms. One such mechanism first discussed in physical–chemical phraseology is through an immunologic response[3,4]. An optimum response will inhibit growth, but an excessive response (massive) produces an antibody halo (film) about the particle matrix (antigen). The presence of sufficient numbers of such intermeshed matrixes produces the structured (coagulated) pathological site (*immunosuppression*). This immunological mechanism is presented as plausible in the responding letter[1], and we agree since we originated it[4]. The presence of a virus as being essential in every case of triggering a neoplasm is still widely under investigation. Alternative routes of pathology are also possible, especially considering the fact that tumors can have induction periods of many years.

The abnormal matrix developed by any of the mechanisms would be expected to provide an environment in which the normal biochemical reactions would be radically altered. Further, carcinogenesis in such an abnormal matrix might even be the result of enzyme induction or a damaged feedback mechanism that fails to prevent a continuous production of extracellular macromolecules. The pathological mechanism proposed for the extracellular phase can also occur in the cytoplasm. The gel-like structures of the internal organelles are particularly susceptible to matrix distortion by particles such as chemicals and viruses. These are among the many possibilities that fit the hypothesis. Using this concept of a tumor as cells coagulated in a coacervated matrix suggested the use of matrix structure breakers as therapeutic agents. This approach, consistent with our hypothesis, is showing early promise[7,9,10].

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Simplified Drug Transport Scheme

The following suggestions concern the *Theoretical* section of the recent article "Potential of Liquid Membranes for Drug Overdose Treatment: *In Vitro* Studies"[1]:

1. The symbol C_e^o should be C_o.
2. Equation 3 should be clarified.
3. A simplified scheme to describe the transport of acidic drug from the donor phase (pH 2) to the central aqueous phase of liquid membranes (pH 12) should be formulated into at least three major steps:

(*a*) Partition of unionized drug (HA) between the oil phase and the aqueous phase (pH 2):

$$P_{\mathrm{I}} = \frac{C_o}{C_e} \qquad \text{(Eq. 1)}$$

where P_{I} is the apparent partition coefficient of unionized drug (HA) between the oil phase and the aqueous phase (pH 2) and C_o is the concentration of drug in the oil phase of the membrane before diffusion.

(*b*) Diffusion of drug across the membrane.

(*c*) Partition of diffused unionized drug (HA) between the oil phase and the central aqueous phase (pH 12):

$$P_{\mathrm{II}} = \frac{C_{\mathrm{I}}}{C_i} \qquad \text{(Eq. 2)}$$

where P_{II} is the apparent partition coefficient of diffused unionized drug (HA) between the oil phase and the central aqueous phase (pH 12), C_{I} is the concentration of drug in the oil phase of the membrane after diffusion, and C_i is the concentration of drug in the central aqueous phase of the membrane.

Therefore, Fick's law of drug diffusion across the membrane may be written as:

$$\frac{dC_o}{dt} = -DA\frac{\Delta C}{\Delta X} \qquad \text{(Eq. 3)}$$

$$\frac{dC_o}{dt} = \frac{-DA}{\Delta X}(C_o - C_{\mathrm{I}}) \qquad \text{(Eq. 4)}$$

Since $C_o = P_{\mathrm{I}}C_e$ and $C_{\mathrm{I}} = P_{\mathrm{II}}C_i$, then:

$$\frac{dC_eP_{\mathrm{I}}}{dt} = \frac{-DA}{\Delta X}(P_{\mathrm{I}}C_e - P_{\mathrm{II}}C_i) \qquad \text{(Eq. 5)}$$

$$\frac{dC_e}{dt} = \frac{-DA}{\Delta X}\frac{1}{P_{\mathrm{I}}}(P_{\mathrm{I}}C_e - P_{\mathrm{II}}C_i) \qquad \text{(Eq. 6)}$$

If $C_e \gg C_i$ and $P_{\mathrm{I}} \approx P_{\mathrm{II}}$, $(P_{\mathrm{II}}/P_{\mathrm{I}})C_i$ can be negligible. Equation 6 can be written as:

$$\frac{dC_e}{dt} = \frac{-DA}{\Delta X}C_e \qquad \text{(Eq. 7)}$$

$$\frac{dC_e}{dt} = -kC_e \qquad \text{(Eq. 8)}$$

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