effects of certain drugs increases with a decrease in the concentration of albumin in plasma (11, 12). Since f increases with decreasing albumin concentration, it has been suggested that the increased incidence of adverse effects of drugs in patients with hypoalbuminemia may be due to decreased binding of such drugs to plasma proteins, among other factors (11, 12). The "average" steady-state concentration of total drug in plasma ($\bar{C}_p$) is:

$$\bar{C}_p = R/\text{total clearance} \qquad \text{(Eq. 3)}$$

where R is the dosing rate (13). Therefore, according to Eq. 1:

$$f\bar{C}_p = R/k'' \qquad \text{(Eq. 4)}$$

which shows that the average steady-state concentration of free drug should be unaffected by a change in f. This effect was demonstrated experimentally (14, 15). Based on these considerations, it has been stated that a change in f should not affect the intensity of pharmacological activity of a drug during the steady state. However, this conclusion is not necessarily correct.

Figure 2 shows the time course of steady-state free drug concentrations for the hypothetical drug described in Fig. 1 under conditions when $f = 0.01$ or 0.03 and V_d is 0.20 or 0.25 liter/kg. While the average concentration of free drug (area under the curve divided by dosing interval) is equal under both conditions, its maximum concentration is substantially higher when $f = 0.03$. Consequently, it is entirely feasible that an increase in f results in an increased incidence of adverse effects[1].

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[1] *Note added in proof:* Consistent with the theoretical predictions in this communication, it was recently reported [R. Gugler and D. L. Azarnoff, *Clin. Pharmacokinet.*, **1**, 25(1976)] that the maximum plasma concentration of free phenytoin is higher and the minimum plasma concentration is lower in nephrotic patients with hypoalbuminemia (phenytoin free fraction = 0.19) than in normal subjects (phenytoin free fraction = 0.10) at the steady state during multiple dosing of phenytoin. The incidence of adverse effects of phenytoin is increased in patients with hypoalbuminemia (12).

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Appearance of Myelin Forms in Rheopexic Dispersions of Dioctyl Sodium Sulfosuccinate

Keyphrases ☐ Dioctyl sodium sulfosuccinate—rheopexic dispersions, formation of micelles ☐ Micelles—formation in rheopexic dispersions of dioctyl sodium sulfosuccinate ☐ Dispersions, rheopexic—dioctyl sodium sulfosuccinate, formation of micelles ☐ Rheopexic dispersions—dioctyl sodium sulfosuccinate, formation of micelles ☐ Surfactants—dioctyl sodium sulfosuccinate, rheopexic dispersions, formation of micelles

To the Editor:

The detection of long tubular structures visible under the electron microscope has been reported for aqueous dispersions of many phospholipids (1). These observable structural units have been described variously as "myelin forms" and "micelles." Stoeckenius (2) and Fernandez-Moran (3) detected, identified, and described myelin forms of phospholipids under the electron microscope at magnifications of 400,000–1,250,000×.

During work on the development of rheopexy in dispersions of dioctyl sodium sulfosuccinate in normal saline (4), the pronounced development of myelin forms was observed under the light microscope at 430× after a shear stress was applied. The dispersion consisting of

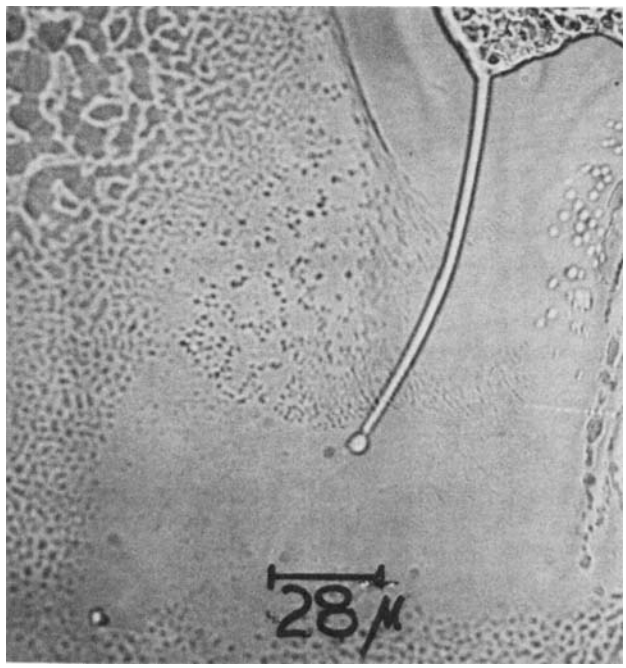

Figure 1—*Single tubular body thought to be a myelin form or micelle (430×).*

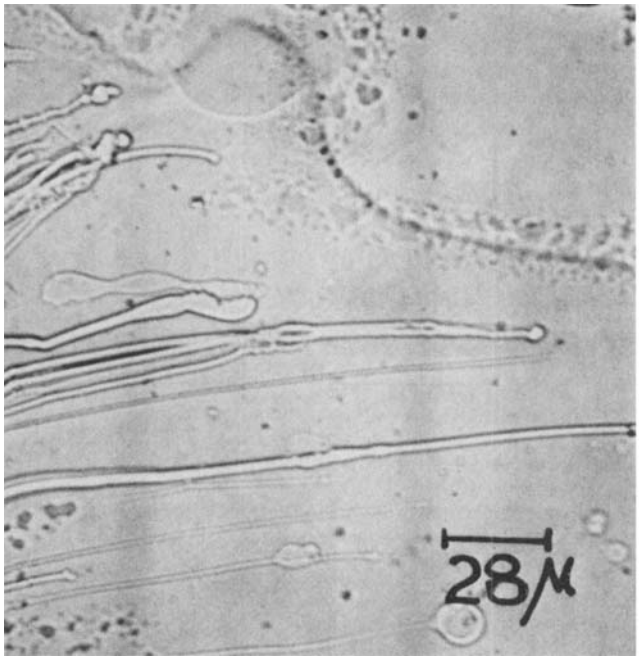

Figure 2—*Elongated and multiple myelin forms (430×).*

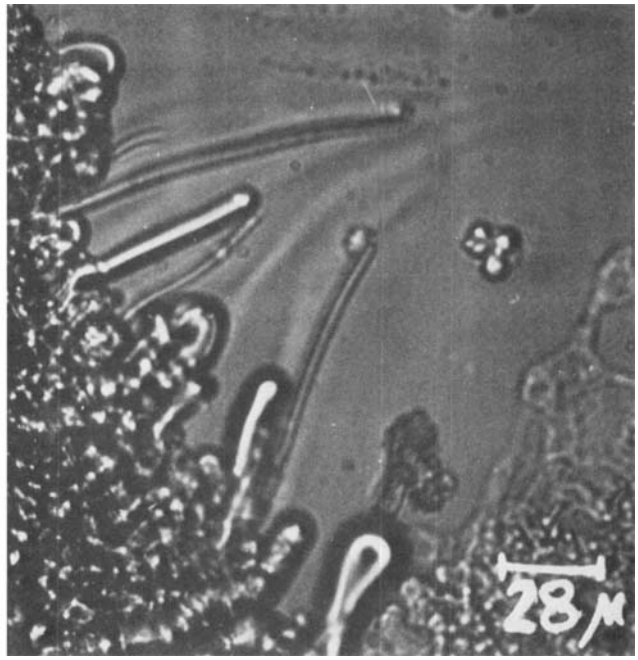

Figure 3—*Myelin forms exhibiting optical birefringence (430×).*

10% (w/v) dioctyl sodium sulfosuccinate in 0.9% NaCl developed the greatest degree of rheopexy as well as a large number of observable myelin forms. Similar concentrations of the surfactant in distilled water failed to produce the rheopexic quality or the myelin forms. Figures 1–3 illustrate the morphology of the structural units observed in the 10% (w/v) dioctyl sodium sulfosuccinate dispersion in normal saline.

From a purely speculative consideration, we felt that the development of the rheopexic character (*i.e.*, the increase in viscosity under shear stress without a concomitant volume dilation) in dispersions of dioctyl sodium sulfosuccinate in saline was due to a shear stress-induced aggregation of small micelles into large micellar units. The detection of long "strand-like" tubular bodies in rheopexic dispersions of dioctyl sodium sulfosuccinate in saline gives credence to this speculation.

Figure 3 illustrates myelin forms exhibiting optical birefringence. The observed phenomenon of optical anisotropy, which occurred only after a shear stress was applied, indicates the formation of a spontaneously oriented, highly structured system which develops with the shear stress and/or saline environment (5). This optical phenomenon has been described in the literature (5, 6) for some colloidal dispersions which exhibit structuring upon stirring, such as in the formation of "tactoids" of ferric hydroxide and tungsten trioxide.

The significance of the formation of such large micellar units or myelin forms is far reaching from a thermodynamic view. From an entropy consideration alone, the spontaneous structuring of surfactant molecules into the observed large structural units, due ostensibly to a favorable saline concentration and shear stress, escapes traditional explanation.

Furthermore, as Stein (7) suggested, and we concur, the structure of these myelin forms may have an important bearing on an understanding of animal cell membrane origin and structure.

Our observation that a nonphospholipid surfactant can spontaneously form large structural units, under proper conditions of shear stress and salinity, gives apparent credence to the supposition that there exists a chemical nonspecificity in the formation of myelin forms. The formation of such structural bodies may be an indication of a previously unknown general physical characteristic of surface-active agents under the influence of salinity and shear stress.

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