

after five weeks the phenylmercuric nitrate concentration had fallen to  $10.0 \mu\text{g/ml}$  with a corresponding reduction in antibacterial activity. Control solutions containing phenylmercuric nitrate only, showed no reduction in concentration or activity.

*Heat experiments.* Ampoules containing a solution of phenylmercuric nitrate ( $20.0 \mu\text{g/ml}$ ) with sodium metabisulphite ( $1.0 \text{ mg/ml}$ ) were assayed after (a) exposure to a temperature between  $98^\circ$  and  $100^\circ$  for increasing periods of time and (b) autoclaving ( $115^\circ$ , 30 min). The phenylmercuric nitrate concentration in (a) fell rapidly; after thirty minutes only  $5.0 \mu\text{g/ml}$  remained and the antibacterial activity had diminished. In case (b) the presence of neither phenylmercuric nitrate nor antibacterial activity could be demonstrated. Controls in both cases showed no reduction in concentration or activity.

The use of phenylmercuric nitrate as a preservative has been criticized on other grounds (Brown & Norton, 1965; Norton, private communication), and the above results give further weight to the argument for its discontinuance. More disquieting, however, were the results obtained in examining heat-sterilized official eye drops and injections formulated to contain both phenylmercuric nitrate and sodium metabisulphite. Whether prepared at this School or purchased from reputable manufacturers, only negligible amounts ( $<1.0 \mu\text{g/ml}$ ) of phenylmercuric nitrate could be detected, and no antibacterial action could be demonstrated.

No official test is specified to ensure the antibacterial activity of added preservation in eye drops or injections. This may explain why the inactivation of phenylmercuric nitrate by sodium metabisulphite has not hitherto been reported.

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#### Progress towards a standard to limit particulate contamination in intravenous fluids

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Instrumental methods for detecting unwanted undissolved solid particles in intravenous solutions are more objective than the visual inspection methods at present in use.

Following the observation that there is usually a log-log relation between particle size and cumulative number, Groves (1969) proposed a standard written in the form-specific value  $(S) = (\log N_{1.0} - 2.5)/M$ , where  $N_{1.0}$  is the estimated number of particles at a threshold of  $1.0 \mu\text{m}$ , and  $M$  is the slope of the log-log distribution. This takes into account the fact that the numbers of particles and the slopes of the distributions varied widely from container to container, even those from the same batch, and is not confined to one instrumental method or principle of detection.

The response of a number of Coulter machines to both a square wave generator and to a standardized suspension of a polystyrene-DVB latex (mean diameter  $8.25 \mu\text{m}$ ) was measured. The standard error was  $\pm 0.31\%$  of the mean response to the square wave generator for eleven machines, and  $\pm 1.96\%$  of the mean count on the suspension for twelve machines. Provided suitable calibration materials were available it is suggested that the main obstacles to a collaborative trial of this instrument could be overcome.

The validity of the log-log relation between the numbers of contaminating particles and particle size was confirmed up to  $30 \mu\text{m}$  using a HIAC Model P305-SST Automatic Particle Counter (Carver, 1969). The HIAC instrument was unable to count at levels exceeding 3000/ml. Since, in good quality intravenous solutions encountered in practice, counts rarely exceed 50 particles per ml at a threshold of  $5.0 \mu\text{m}$  (e.g. Appino & Robinson, 1969) this limitation on counting rate is unlikely to constitute a problem.

Four bottles rejected from a hospital-made batch of Sodium Chloride Injection B.P. because of the presence of visible particles were examined using both the Coulter Counter and the HIAC instruments. Coulter counts were made using the device described earlier (Groves, 1969). The bottle was then disconnected and attached to the receiver of the HIAC. Replicate counts were taken on successive 40 ml volumes until the bottle contents had been used up.

Specific values measured were as follows:—

Bottle number	1	2	3	4
Coulter	0.70	0.62	0.62	0.64
HIAC	0.68	0.62	0.61	0.68

It is concluded that the two instruments are broadly comparable, and are suitable for the purpose of counting particulate contamination in intravenous solutions.

Collaboration between different laboratories is required to establish the utility of this approach to the problem of assessing contamination, and to devise a realistic standard of cleanliness.

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#### Some investigations of the effect of a non-ionic surfactant on the diffusion of hydrocortisone across a cellulose acetate membrane

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The authors report further studies of the effects of non-ionic surfactants upon the diffusion of steroids across a cellulose acetate membrane. Diffusion rates have been measured using the 'short' and 'ultra-short' time methods recently developed (Short, Abbs & Rhodes, 1970; Short, Jenkins & Rhodes, unpublished); the apparatus was also described in these publications. The temperature dependence of the diffusion rate has been examined in systems with and without n-alkyl polyoxyethylene surfactant. In all cases the Arrhenius equation was obeyed, e.g. correlation coefficient for five temperatures 0.997. The diffusional energies,  $\Delta H_d$ , and entropies,  $\Delta S_d$ , have been calculated, following the method of Barrer (1939). In distilled water the values were estimated to be  $36.0 \times 10^3 \text{ J mol}^{-1}$  and  $-3.4 \times 10^2 \text{ J deg}^{-1} \text{ mol}^{-1}$  respectively.

The enthalpy,  $\Delta H_b$ , and entropy,  $\Delta S_b$ , of micellar binding, calculated by previously described methods (Molyneux, Rhodes & Swarbrick, 1965; Humphreys & Rhodes, 1968; Molyneux & Rhodes, unpublished), were found to be  $-17.6 \times 10^3 \text{ J mol}^{-1}$  and  $-22 \text{ J deg}^{-1} \text{ mol}^{-1}$  respectively.

Interpretation of the diffusion and micellar binding results has led to the development of a simple thermodynamic hypothesis. This can explain how surfactants can both increase and decrease diffusion rates even when, as in the systems investigated in this work, the surfactants do not modify membrane permeability by direct interaction with the membrane. From the micellar binding data values of  $\Delta H_d$  and  $\Delta S_d$ , with 2%  $C_{16}E_{30}$  solutions on the donor side of the membrane, have been predicted. The agreement between the predicted and experimental values is good,  $\Delta H_d$   $53.9$  (expt  $50.9$ )  $\times 10^3 \text{ J mol}^{-1}$   $\times 10^3$ ,  $\Delta S_d$   $-3.1$  (expt  $-2.9$ )  $\times 10^2 \text{ J deg}^{-1} \text{ mol}^{-1}$ .

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