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Some size distributions of particulate contamination found in commercially available intravenous fluids

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The size distributions of particulate contamination found in some commercially available normal saline solutions and dextrose solutions have been determined using the Coulter Counter. Many of these solutions contain considerable numbers of particles larger than the equivalent volume diameter of erythrocytes. Earlier observations that most of the particulate contamination emanates from the rubber closure were confirmed by repeated autoclaving of saline in a rubber-plugged glass container. It is possible to prepare solutions substantially free of particles larger than 5 μ, and commercial material of this quality is available. A tentative standard is proposed and discussed.

A RECENT *Lancet* annotation (1965) discussed the particulate contamination of intravenous injection fluids and drew attention to the work of Garvan & Gunner (1963, 1964). These authors detected particles suspended in the fluids by means of a dark ground illumination technique and described a membrane filtration method for the collection of the contamination before subsequent microscopic examination and identification. They pointed out that official standards for particles in intravenous fluids are entirely inadequate, and made suggestions for the allowable limit of contamination.

Schmitt (1964) also described a similar membrane filtration technique. He concluded that the major disadvantages of the method were that it was difficult to attain and retain control standards, and that the microscopical scanning was slow and tedious.

Groves & Major (1964), discussing methods of assessing particulate contamination, suggested that the Coulter Counter was an ideal instrument for this purpose in electrolytes. Normal saline for injection from commercial sources was examined and shown to vary widely in quality. This experimental work has now been extended to other intravenous fluids and the particle size of the particulate contamination investigated.

Experimental

MATERIALS AND METHODS

The experimental method is based on that described by Groves & Major (1964). A Coulter Counter Model A (Industrial) was employed, fitted with a 70 μ orifice tube. The instrument was previously calibrated with pollens and monosize polystyrene emulsions of known particle diameter (equivalent volume diameter). Counts were made of each sample at instrument thresholds corresponding to known sizes. As the instrument counts all particles above a threshold, the threshold was progressively raised from 1·5 μ until the count fell to a value of 20 particles/ml. The results are given as cumulative over-size curves, plotting the logarithm of the count/ml as a function of the threshold (particle diameter).

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Results

NORMAL SALINE

Groves & Major (1964) reported the counts of particles above 1·3 μ. Size distributions obtained on samples from similar commercial sources are shown in Fig. 1.

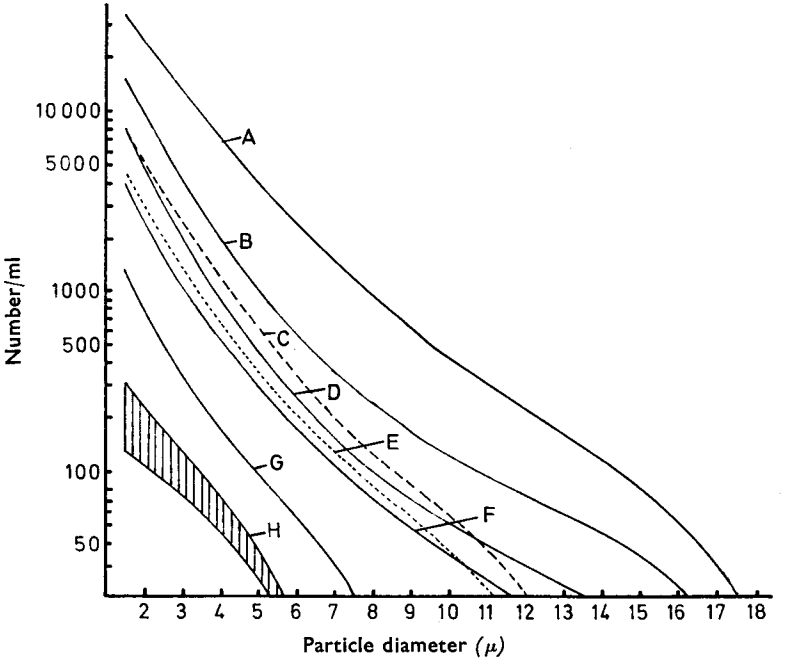

FIG. 1. Particle size distributions of particulate contamination in normal saline. A. Plastic bag, with giving set (counts of saline taken directly from bag identical to those taken after passage through the giving set). B, C, D. Rubber-plugged glass bottle, three samples from same source. E. Rubber-plugged glass bottle. F. Plastic bottle, rubber over-seal. G. Plastic bag, rubber closure. H. Range of counts found in saline from plastic ampoules (Polyfusor).

DEXTROSE (5%)

Dextrose solutions do not contain electrolyte, which must therefore be added before examination on the Counter. A 4·0% sodium chloride solution was passed repeatedly through a Millipore G.S. membrane filter and the size distribution of remaining particles measured on the Counter. This solution was diluted 1 in 4 with the dextrose solution under examination and the mixture counted on the instrument as before. If n_s = number of particles/ml above a given size and n_t = number of particles in the saline-dextrose mixture, the number of particles (n_d) present in 1 ml of undiluted dextrose solution is given by

$$n_d = 4/3\ n_t - 1/3\ n_s$$

Some results obtained on commercially available transfusion fluids are shown in Fig. 2.

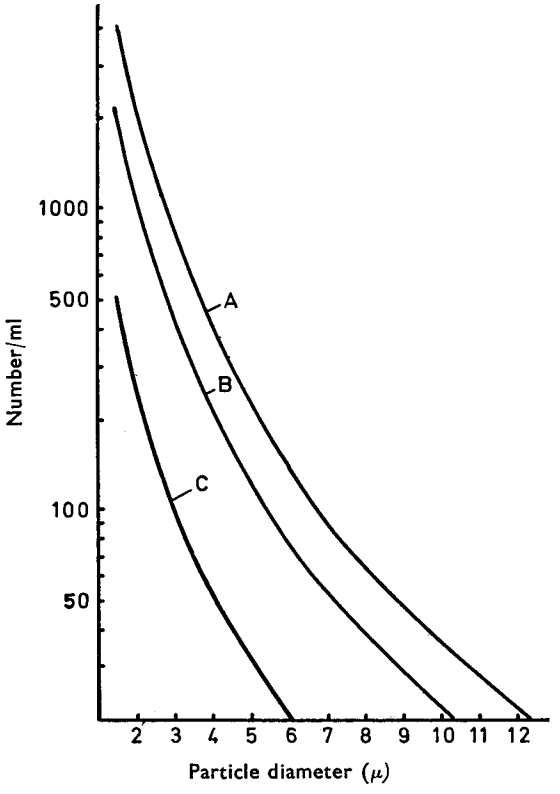

FIG. 2. Particle size distributions of particulate contamination in 5% dextrose solution. A. Rubber-plugged glass bottle (Manufacturer A). B. Rubber-plugged glass bottle (Manufacturer B). C. Plastic ampoule (Polyfusor).

OTHER TRANSFUSION FLUIDS

It was not practicable to examine more than a few of the many different transfusion fluids available. Solutions of electrolytes can be examined directly but non-electrolytes require dilution with electrolyte as described under dextrose. The Counter requires recalibration for each electrolyte system since the conductivity differs, but it was noted that the instrument calibration factors did not vary widely with 0·9% saline or Ringer–Lactate solution. For this investigation it was sufficient to regard the conductivity as being unchanged. Some direct counts, at one threshold only, illustrate the application of the method: particle counts/ml, $>$ ca. 1·5 μ, on miscellaneous intravenous injection fluids, all packed in a plastic ampoule pack (Polyfusor) were, for 1/6M sodium lactate, 696; Hartmanns solution, 398; dextrose saline, 660; sodium sulphate, 495.

THE EFFECT OF REPEATED AUTOCLAVING

New bottles and closures were cleaned by the usual methods and allowed to drain dry. A bulk quantity of filtered normal saline solution

was prepared and filled in 500 ml quantities. For control purposes similar bottles were filled and closed by rubber plugs covered with Saran film (Dow). Plastic ampoules were also filled with the same solution although these are disposable and would normally not be re-used. All the filled containers were sterilised by autoclaving (10 lb/in^2 pressure for 35 min) and total counts were recorded for samples taken from each container between each successive heating. The mean counts from four containers of each type are shown in Fig. 3 as a function of the number of sterilisation cycles.

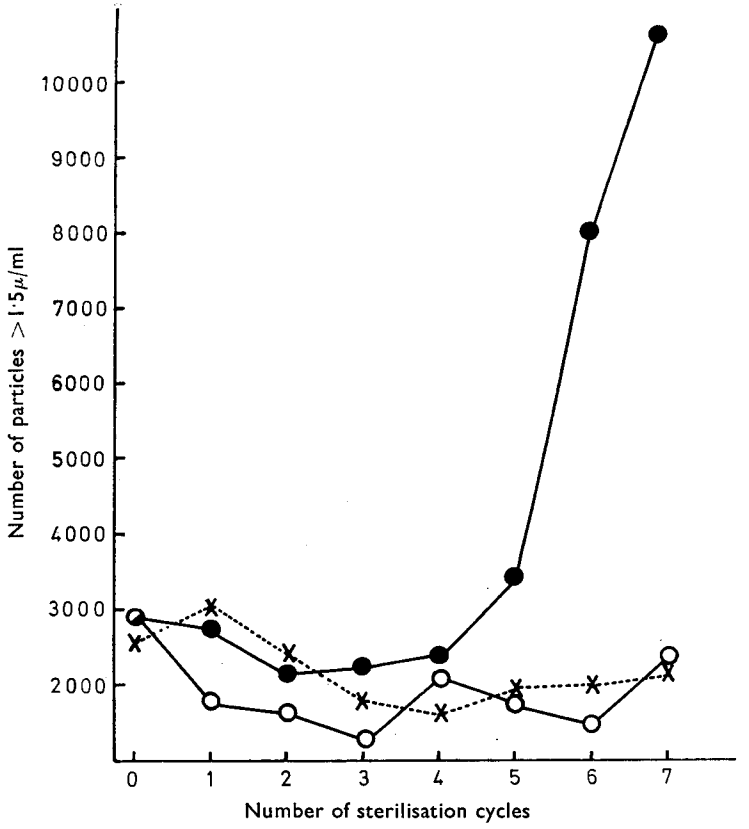

FIG. 3. The effect of repeated autoclaving on the particulate counts of normal saline. ● Rubber-plugged glass bottle. ○ Saran covered rubber-plugged glass bottle. X Plastic ampoule.

EFFECT OF FILTRATION

Groves & Major (1964) suggested that the Counter might be applicable to the routine control of the filtration process during the preparation of a transfusion solution. Sodium chloride B.P. was dissolved in freshly distilled water for injection and 1 litre passed through each filtration

medium to wash the filter before taking a sample for size analysis. The filter media were selected as being representative of types commonly used for the clarification of intravenous fluids in industrial and hospital laboratories; they were not supported by sintered glass filters to remove particles washed off the candle and asbestos pad. Results are shown in Fig. 4.

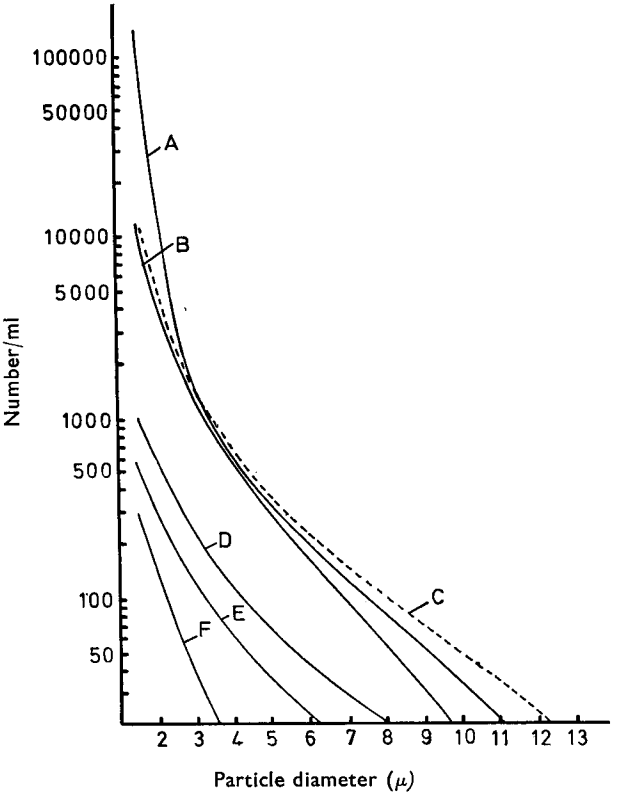

FIG. 4. The effect of filtration through various media upon the particle size distribution of material in 0·9% sodium chloride solution. A. Unfiltered. B. Sterilising asbestos pad. C. Sterilising unglazed porcelain candle. D. No. 4 sintered glass filter. E. Millipore H.A. membrane. F. Millipore G.S. membrane.

Discussion

All the samples of commercial origin examined were from reputable sources and were believed to be of recent manufacture. Although there are widely differing degrees of particulate contamination these are probably representative of material hitherto considered satisfactory for intravenous use. In most instances only one sample has been taken on a purely random basis. Nevertheless, it is possible that a patient might

sample material which is contaminated to the same degree as, say, sample A of Fig. 1.

There seem little doubt, following the work of Garvan & Gunner (1963, 1964), that most particles in an intravenous fluid emanate from the rubber closure. This is substantiated by Groves & Major (1964) and by the results shown in Fig. 3. The pack for an intravenous fluid is therefore of paramount importance. As shown in Figs 1 and 2, some commercial solutions contain very few particles above 5 μ.

In the assessment of particulate contamination, the Coulter Counter proved rapid and objective. Moreover, in one or other form, it is to be found in many hospital pathology departments and industrial laboratories. The instrument could be applied to non-electrolyte transfusion fluids by the dilution technique described for dextrose solution and seems to be ideally adapted to this problem.

However, it is necessary to determine the significance of the particulate contamination, especially the hazard presented to the patient, in order to suggest suitable and practicable standards. Groves & Major (1964) suggested that the nearer the approach to a particle-free solution the less likely is any possible hazard. Garvan & Gunner drew attention to granulomatous reactions produced in rabbits and in humans by cellulose particles. Other materials may be more or less reactive and it is obviously desirable to limit all particulate contamination as far as possible.

The significance of the particle size distribution is even less certain. Stehbens & Florey (1960) described the formation of thrombi after the injection of submicron particles into observation chambers in rabbits ears. It would also appear to be undesirable to inject large numbers of particles of the same order of size as an erythrocyte which, on the Coulter Counter, has a mean equivalent volume diameter of approximately 4·5 μ (Brecher, Schneiderman & Williams, 1956). Chances of embolic phenomena occurring clearly increase with particles above 5 μ diameter.

The data presented in Fig. 4 show that it should be possible to filter out most particles above 5 μ. In practice, much larger volumes would be passed through a filtration medium and the particle size distribution would be expected to decrease as the pores within the medium become filled. An arbitrary upper size limit of 5 μ should therefore be a workable standard for the filtered solution before packing.

If an arbitrary limit was set to exclude all particles above 5 μ this could readily be checked by all models of the Counter. A count of 20–30 particles/ml at the threshold corresponding to this size can be regarded as insignificant. With a suitable orifice tube the Model A Counter will detect material of 0·2 μ diameter but it is not certain if a practicable standard could be set at this level. It would appear from Figs 1 and 2 that any sample with a small upper particle size also contains relatively fewer particles at the lowest size-range counted. It is therefore suggested that, for the present, particulate contamination could be limited by specifying that an intravenous injection fluid should contain not more than, say, 50 particles/ml above 5 μ.

References

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