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Reduction of absorption of drugs into TPN plastic containers by phospholipids and fat emulsions

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Summary

The absorption of a model compound, rhodamine B, into TPN plastics, has been studied using direct spectroscopic measurement of the concentration of dye in the plastic film. It was found that uptake of the dye was decreased by the addition of albumin, egg phospholipids and parenteral fat emulsions ('Intralipid 20%'). Ultrafiltration of solutions of rhodamine B containing these additives suggested that albumin exerted its effect by binding the dye, whereas phospholipids and fat emulsions did not appear to bind rhodamine significantly. It is possible that phospholipids could exert their effects on absorption by forming a barrier layer on the plastic film. However, attempts to detect the adsorption of fluorescent phospholipids on to plastic films were unsuccessful.

Introduction

It is common practice to administer drugs i.v. from plastic containers holding several hours' supply of infusion admixed with other drugs or components for nutrition. The bags are usually made from poly-(vinyl chloride) (PVC), ethylene vinyl acetate polymer (EVA) or polyethylene. A problem with this form of therapy is the loss of active drug by sorption by the polymer of the infusion set. The problem is well-known in the case of several drugs, e.g. diazepam (Kowaluk et al., 1981; Parker et al., 1979), glyceryl trinitrate and other organic nitrates (Roberts et al., 1980; Yuen et al., 1979), insulin (Weisenfeld et al., 1968), phenothiazines, etc, where large losses can occur between the infusion bag and the point of administration, and may also be severe for the bioactive peptides (e.g. secretin (Bitar et al., 1978)) which are currently being investigated for potential therapeutic use. Similar problems occur when drugs in solution are packaged into polymer containers for extended storage periods; the problem may be more marked since the time available for loss is extended. The absorbed drug can alter the properties of the plastic; e.g chlormethiazole plasticizes PVC bags; this may facilitate its absorption, or even accelerate that of other drugs in the solution (Kowaluk et al., 1984). In addition, more volatile substances such as organic nitrates can evaporate through the plastic and evaporate completely.

Previously it has been the practice to evaluate the problem by assaying the loss of drug from the solution which has been exposed to the polymer surface (see e.g. Roberts et al., 1983; Nation et al., 1983; Petty and Cunningham, 1974). There are a number of potential problems with this approach,

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the major one being that all drug loss routes are lumped and assigned to sorption processes. This may cause major errors since the drug may be subject to alternative loss pathways such as oxidation or hydrolysis.

Introduction of modern optical spectrometers with powerful data handling facilities has allowed the study of a wide range of difficult samples and it is now possible to measure the concentration of absorbed species directly in the plastic film. If the degree of absorption is not large, direct measurement of absorbed concentration avoids the need to accurately measure small changes in the solution concentration. We have investigated drug absorption using direct ultraviolet spectroscopic assay of the dye rhodamine B as a model compound in the plastic film. Additionally, we have studied the action of two common TPN mixture components, albumin and lecithin, and the effect of intravenous nutrition emulsion ('Intralipid') on the absorption process.

Materials and Methods

Rhodamine B and bovine serum albumin were purchased from Sigma. Egg lecithin (Lipoid E80 i.v. grade) was kindly donated by Lipoid KG. Total parenteral nutrition bags (3-litre PVC bags, batch 810720U5, Travenol Laboratories Ltd.) and Intralipid 20% (Kabi-Vitrum) were obtained from the Queen's Medical Centre hospital pharmacy.

Strips of plastic 1 cm × 5 cm were cut from the bags, taking care to note and not touch the inner face. These were then floated, inner face down, on the test dye solutions in covered Petri dishes. Strips were removed at suitable intervals, rinsed rapidly with 3 changes of distilled water, blotted dry on clean tissue, and placed directly in the spectrometer (Kontron Uvikon 860) for ultraviolet assay. Background spectra were recorded from plastic films which had been floated on distilled water; these spectra were subtracted digitally rather than used as double-beam references since this led to a better suppression of instrument errors. Plastic films were discarded after measurement rather than re-exposed to the solution, so an absorption–time curve would be built up from several separate strips of plastic rather than by exposing a single strip repeatedly to solution.

Test solutions consisted of distilled water containing rhodamine B (10^{-4} M) to which was added bovine albumin, Intralipid 20%, or egg lecithin. This latter was added as a suspension of small unilamellar vesicles produced by sonicating a suspension of the lipid (Dawe Soniprobe 7532B; 10 minutes × 60W).

The absorption was not found to vary significantly with pH over the range 4–7; however, the pH of the dye solutions was checked to lie in the range 6–8 for all solutions.

Ultrafiltration was performed using ultrafiltration cones (m.w. cutoff 25,000; Amicon Corp.) in a bench centrifuge (2000 rpm for 5 min).

Results

Fig. 1 shows the absorption of rhodamine B into PVC as a function of time. The curve, initially steep, continued to rise for the duration of the experiment. Addition of bovine serum albumin or egg lecithin (10 g/litre) resulted in the much lower absorption shown as a function of time in Fig. 2.

Fig. 3 shows the reduction in dye absorption as a function of albumin concentration after 3 h exposure of the plastic. Addition of 10 g/litre of albumin caused the absorption to be approximately halved. A similar effect was observed with egg lecithin, added as a suspension of liposomes (Fig. 4); 10 g/litre caused absorption to be reduced to approximately one third of its original value.

Since phospholipids are used as emulsifiers in parenteral nutrition emulsions, it is reasonable to suspect that these emulsions may also influence the absorption of drugs into plastic films. Fig. 5 shows the effect of adding up to 50% of 'Intralipid 20%' to the test solution. The dye absorption was reduced to approximately 40% of its value in the absence of the fat emulsion. It should be stressed that all solutions were 10^{-4} M in rhodamine B; the effect was not due to dilution of the dye solution with the emulsion.

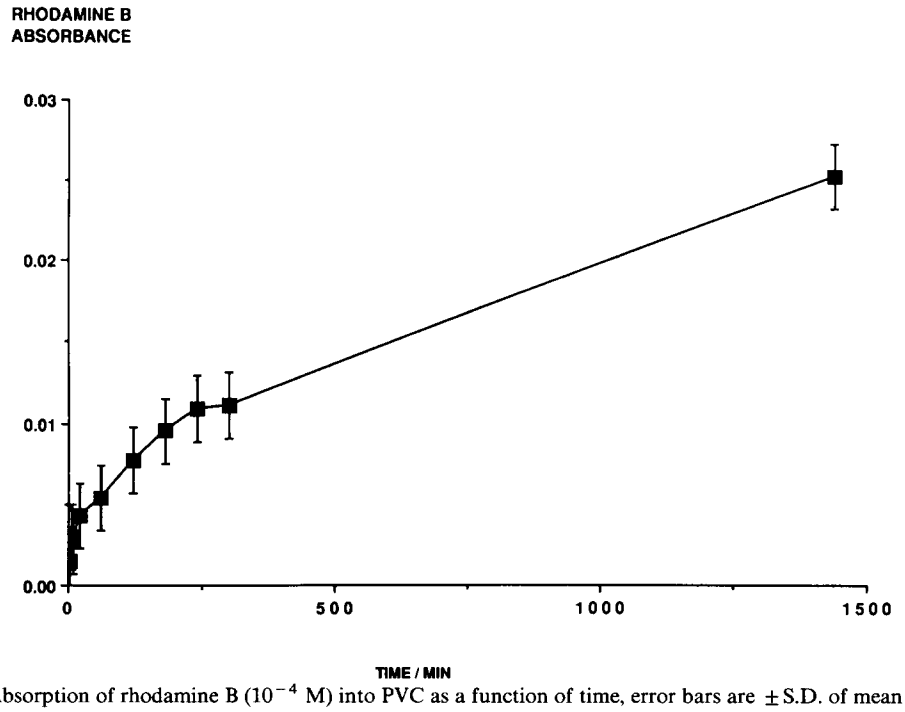

Fig. 1. Absorption of rhodamine B (10^{-4} M) into PVC as a function of time, error bars are ±S.D. of mean values.

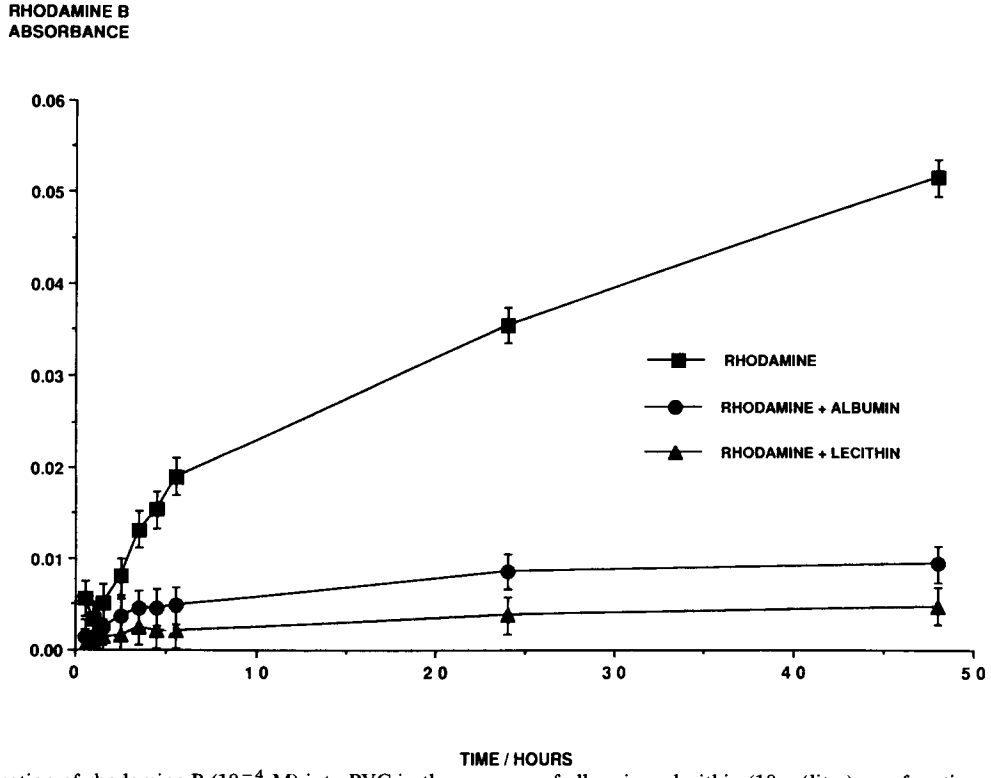

Fig. 2. Absorption of rhodamine B (10^{-4} M) into PVC in the presence of albumin or lecithin (10 g/litre) as a function of time; error bars are ±S.D. of mean values.

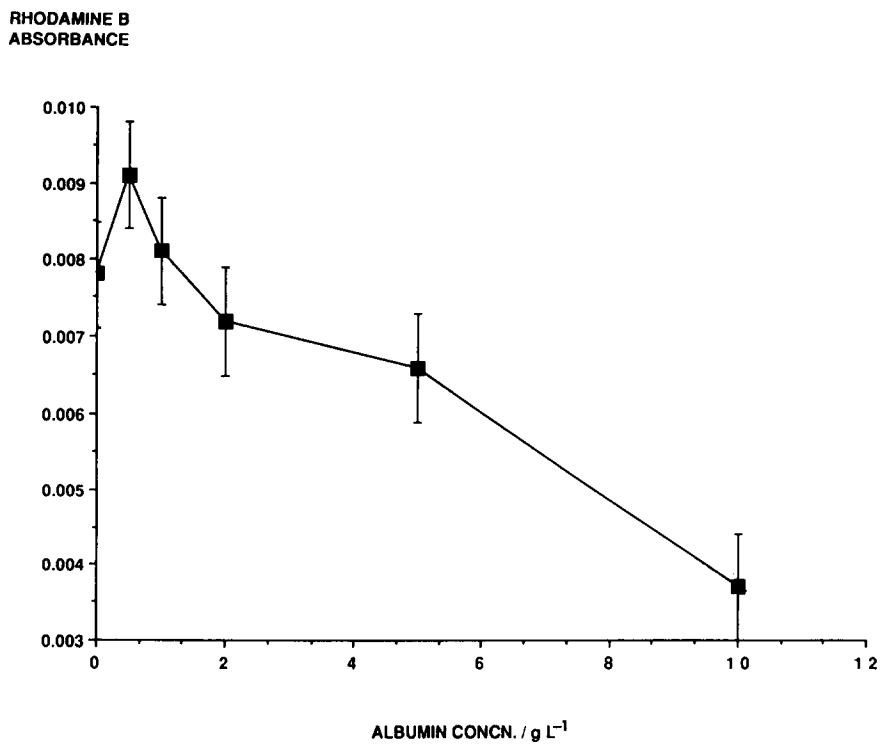

Fig. 3. Absorption of rhodamine B into PVC as a funcion of albumin concentration after 3 h exposure; error bars are ±S.D. of mean values.

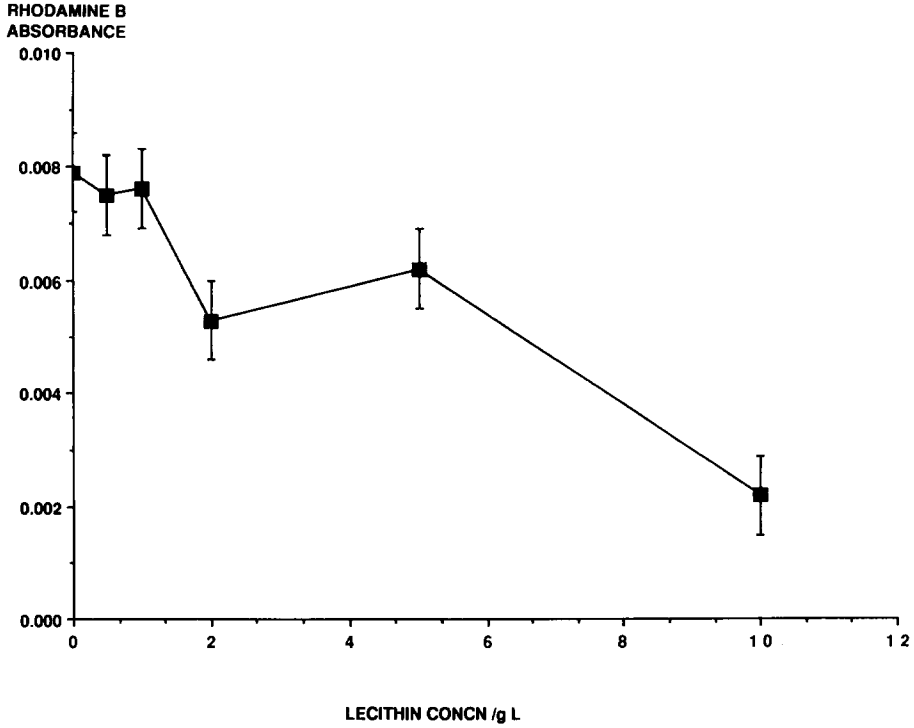

Fig. 4. Absorption of rhodamine B into PVC as a function of egg lecithin concentration after 3 h exposure; error bars are ±S.D. of mean values.

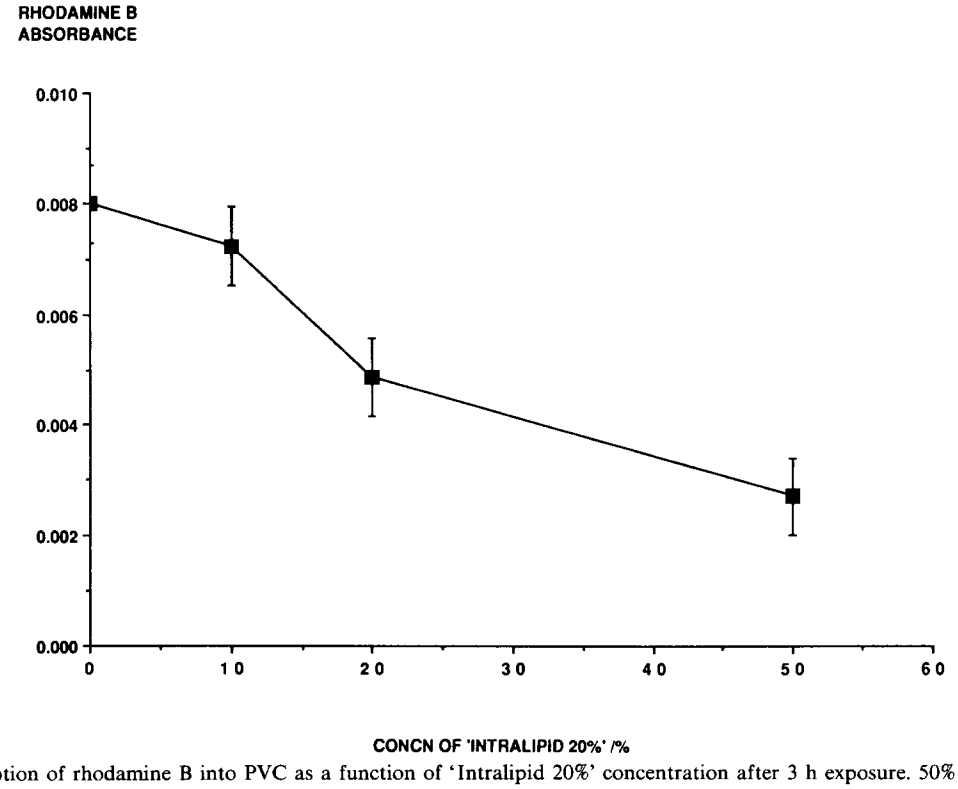

Fig. 5. Absorption of rhodamine B into PVC as a function of 'Intralipid 20%' concentration after 3 h exposure. 50% concentration corresponds to a 1 : 1 dilution of 'Intralipid 20%' or an oil phase volume of 10%; errow bars are ±S.D. of mean values.

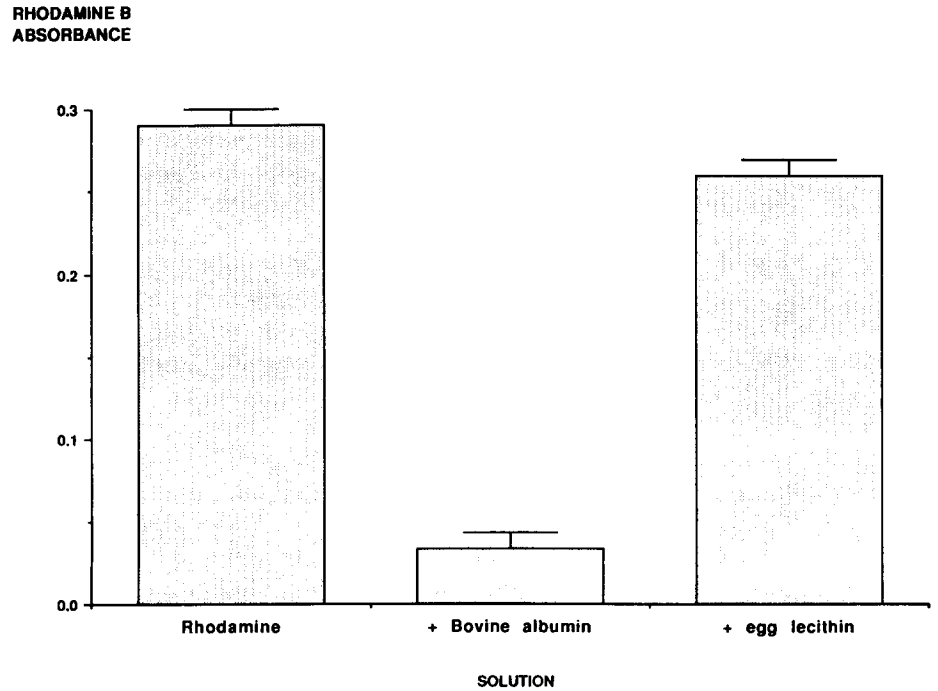

Fig. 6. Absorbance of rhodamine B solutions after passage through a 25000 mW cutoff ultrafiltration membrane, in the presence and absence of albumin and egg lecithin; error bars are ±S.D. of mean values.

In order to assess the possible role of binding of rhodamine B to albumin or phospholipids, the dye solutions were subjected to ultrafiltration. The results (Fig. 6) show that rhodamine B in the presence of phospholipids was not retained by the ultrafiltration membrane to a significantly greater extent than the free dye; however the addition of albumin caused a considerable reduction in the amount of dye able to pass through the membrane. The corresponding experiment to assess binding of dye to 'Intralipid 20%' oil droplets could not be performed, since the emulsion caused immediate blockage of the ultrafiltration membrane.

Finally it should be noted that attempts to measure the adsorption of phospholipids on to PVC surfaces using the fluorescent probes β-(pyren-1-yl)-decanoyl-γ-palmitoyl-l-α-phosphatidylcholine and *N*-4-nitrobenzo-2-oxa-1,3-diazole-1-α-phosphatidylethanolamine were unsuccessful; significant adsorption has not yet been detected using this technique.

Discussion

Rhodamine B is a molecule with balanced hydrophilic/hydrophobic properties and as such is a good model for many drugs which may be coadministered with TPN mixtures. The dye was initially absorbed rapidly, and ultimately more slowly, suggesting attainment of saturation, in agreement with the hypothesis (Polack et al., 1979; Yuen et al., 1979) that permeation is essentially a partition-controlled process. As such any process which lowers the activity of the dye in solution would be expected to reduce the absorption.

Bovine albumin is well known to reduce the absorption of insulin (Weisenfeld et al., 1968; Petty and Cunningham, 1974) to TPN bags, and also the absorption of secretin (Bitar et al., 1978). However, the proposed mechanism of action in these cases is the competitive blocking of peptide/protein binding sites on the plastic surface by the albumin. It is surprising that a hydrophilic species such as albumin should bind to a hydrophobic surface such as PVC; this may be rationalized by the proposal that the surface contains hydrophilic binding sites for the peptide or protein.

Albumin is well known to contain binding sites for many drugs which have been well investigated, largely by spectroscopic methods (see e.g. Zia and Price, 1976). The inability reported here for rhodamine to pass through an ultrafiltration membrane in the presence of albumin suggests an alternative mechanism for the prevention of absorption, i.e., that albumin binds rhodamine in a similar manner to other species. This reduces the activity of rhodamine in solution and hence decreases absorption. Further studies are required to assess the relative importance of these two mechanisms.

Phospholipids appear to have a similar absorption-reducing effect in these systems. This is unusual, since it is unlikely that phospholipids could be capable of binding drugs or the model dye used here. This is supported by the ultrafiltration data, which demonstrate that rhodamine passes through the filter as easily in the presence of phospholipid liposomes as in their absence. The lipids used were added as suspensions of small unilamellar vesicles to increase the available lipid surface area, and thus maximize any binding observed. Nevertheless, the concentration of rhodamine passing through the ultrafiltration membrane in the presence of phospholipids was not significantly different from that passing through in their absence.

A similar effect is observed when parenteral nutrition emulsions were added to the solutions. This is not surprising in the light of the previous result, since fat emulsions contain phospholipid emulsifier in excess of that required to stabilize the emulsion. This is almost certainly present as liposomal structures. The concentrations of fat emulsion used here are clinically relevant, in that the highest concentration range corresponds to an oil phase volume of 10%. Most published TPN regimens contain fat phase volumes of 3–10%.

It may be suggested that the phospholipid prevents the absorption of drug by adsorbing on to the surface of the plastic film and altering its surface properties. We have investigated this possibility by labelling the phospholipid liposomes used with two fluorescent lipids. Pyrenyl PC contains a pyrene group as part of the hydrophobic 1-acyl chain, whereas NBD-PE has the hydrophilic ethanolamine headgroup substituted by

the fluorescent *N*-4-nitrobenzo-2-oxa-1,3-diazole group. It was not possible to detect the fluorescence of either of these species on the surface of the plastic film even after prolonged exposure. Both species are fluorescent in hydrophobic and hydrophilic environments and so this failure cannot be explained by the adsorbed species being in an unsuitable environment. At present the only reasonable explanation appears to be that the absorption of the dye occurs in a small number of sites which can be blocked by an undetectably small quantity of phospholipid. Further spectroscopic and surface studies are in progress to study the nature of the absorption environment and test this hypothesis.

In conclusion, it appears that the absorption of solutes to plastic films is particularly sensitive to the presence of macromolecules and colloidal species in the solution. Addition of surface-active materials and colloids can affect the absorption, apparently to the benefit of the user in the case of the fat emulsions studied here. The technique of assaying the drug directly in the plastic film using spectroscopic methods appears to be of use, particularly in the more complex solutions such as those containing parenteral nutrition emulsions which may otherwise require complex workup prior to assay.

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