Table I—Plasma Peak Concentrations and Relative Bioavailability of Cyclobarbital following Oral Administration of the Three Cyclobarbital Calcium Preparations

Preparation	Mean t_{max} (Range), hr	Mean C_{max} (Range), mg/liter	Mean F_{rel} (Range), %
1. Tablets	1.2 (0.33—3.0)	8.3 (7.3—10.8)	100
2. Tablets	1.2 (0.66—2.5)	8.7 (7.4—10.3)	101 (89—136)
3. Aqueous solution	0.7 (0.25—1.5)	8.3 (5.8—11.7)	78 (64—100)

Although substantial variations in absorption rate and relative bioavailability were observed between individuals (see range values), the rank order of these values for the three preparations was generally the same for each volunteer. For one subject, absorption was comparatively slow (t_{max} of 3.0, 2.5, and 1.5 hr for Preparations 1, 2, and 3, respectively), but still the drug was absorbed more rapidly and to a lesser extent when given in aqueous solution.

The present findings clearly indicate that the extent of bioavailability of cyclobarbital in humans is lower when its calcium salt is administered in aqueous solution. This finding is unexpected, whereas the highest absorption rate is in accordance with the usual behavior of an oral aqueous drug solution. It may be argued that after oral administration of barbiturate salts, precipitation of the poorly soluble free acid will occur as soon as the acidic medium of the stomach is reached. This precipitation, however, will also occur for the calcium salt incorporated in the tablets. The precipitate formed after administration of the aqueous solution may have unfavorable redissolution properties in comparison to the precipitate formed after tablet administration. If so, this situation only holds for part of the precipitate, since the rapid absorption of cyclobarbital calcium solution also suggests that rapid (re)dissolution occurs.

A similar observation was made in a separate study when comparing absorption of heptabarbital as free acid with heptabarbital sodium, both from solid dosage forms. The salt showed the highest absorption rate; however, bioavailability relative to the free acid was approximately 20% lower (4). Higuchi *et al.* (5) showed that, in general, salts show higher dissolution rates than the corresponding nonionic drug at any pH, even though the final equilibrium solubility of the drug and its salt is the same. Additional *in vitro* experiments with cyclobarbital calcium are required to study the influence of precipitate formation on the redissolution characteristics of cyclobarbital under acid and weak alkaline conditions.

Although barbiturates are weak acids, their major site of absorption is the intestine (6, 7); therefore, another factor involved in the present findings may be the rate of drug transfer from the stomach to the intestine. However, it is hard to see how this factor could explain the discrepancy between the rate and the extent of cyclobarbital calcium bioavailability from the aqueous solution. Its rapid rate of absorption suggests that rapid drug transfer takes place, which, in principle, favors high bioavailability.

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Fluorocarbon Aerosol Propellants VII: Interaction Studies with Human and Bovine Globulins Using Partition Coefficient Method

Keyphrases □ Fluorocarbon aerosol propellants—interaction with human and bovine globulins, partition coefficient method □ Globulins, human and bovine—interaction with fluorocarbon aerosol propellants, partition coefficient method □ Plasma protein binding—interaction of fluorocarbon aerosol propellants with human and bovine globulins, partition coefficient method

To the Editor:

The partition coefficients of some commonly employed propellants between the aqueous phase and the head space have been shown to be higher in plasma–air systems for humans (1, 2) and other species (2) than in the water (or normal saline)–air system. This finding was postulated to be due to the binding or complexation of these propellants to certain constituent(s) in plasma, as was subsequently confirmed by the partition coefficient method using purified human and bovine albumins (3, 4).

The ability of trichloromonofluoromethane to bind to bovine albumin also was recently demonstrated using a fluorescent probe technique, and these results will be published later. The binding or complexation with other tissue components was also hypothesized to account partially for the high apparent volume of distribution of these neutral propellants in dogs (5).

Table I—Average Partition Coefficients ± *SD* of the Three Propellants in Solutions of Plain Buffer and 5% (w/v) Bovine and Human γ-Globulins

Propellant	Plain Buffer	Bovine γ-Globulin	Human γ-Globulin
Trichloromonofluoromethane	0.298 ± 0.0084	0.273 ± 0.0053 ($p < 0.01$)	0.308 ± 0.0085 ($p < 0.1$)
Dichlorodifluoromethane	0.0916 ± 0.0008	0.0887 ± 0.0017 ($p < 0.05$)	0.0882 ± 0.0013 ($p < 0.02$)
Dichlorotetrafluoroethane	0.0296 ± 0.0009	0.0294 ± 0.0013 ($p < 0.8$)	0.0275 ± 0.0010 ($p < 0.05$)

Since it is important to identify various components of plasma that may interact with these propellants and since γ-globulin has the second highest concentration among various plasma proteins, a preliminary study was conducted on the possible interaction between the three most widely used propellants and human and bovine globulins using the partition coefficient method (3, 4).

The crystallized and lyophilized bovine and human γ-globulins were obtained commercially[1] and were used without further purification. Protein solutions (5% w/v) were freshly prepared in pH 7.4 phosphate buffer (3). The equilibrium study was conducted in a water bath maintained at 21.5–22°. The equilibrium concentrations of the propellants in the aqueous phase were about 0.05, 0.08, and 0.015 mg/ml for trichloromonofluoromethane, dichlorodifluoromethane, and dichlorotetrafluoroethane, respectively.

All propellants were studied individually, and at least four runs were performed on each propellant. The propellant concentrations in both the aqueous phase and the head space in sealed serum bottles were analyzed by a GC method using an electron-capture detector (6). The enhancing effect of *n*-hexane used in the extraction on peak heights in the GC analysis for each propellant was corrected in the calculations (7).

The results of this preliminary study are summarized in Table I. Contrary to the albumin study, all of the partition coefficients in globulin–air systems are only slightly different from those in the plain buffer–air system, indicating an insignificant degree of interaction in spite of statistically significant differences in some systems. The slight decrease of the partition coefficients of some propellants in the globulin solutions is most likely due to the salting-out effect of globulin.

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Novel, Low Cost Approach to Digitizing Tablet Hardness Values

Keyphrases □ Tablet hardness tester—modified to give digitized values □ Digitized tablet hardness values—equipment described

To the Editor:

When formulating tablets with deliberately low hardness values, *i.e.*, <2 kg, it is difficult to determine these values repeatedly and accurately to 0.1 kg on the meter scale of a hardness tester[1]. Shown in Fig. 1 is an inexpensive addition to the hardness tester which will give a digitized reading of these hardness values and print them on an optional printer if desired.

The transducer used for sensing the force applied to break the tablet is a Hall generator[2]. The output signal from a Hall generator is a voltage that is proportional to the current flowing through it and the magnetic flux density (1).

As shown in Fig. 1, a Hall generator is attached to the movable counterweight shaft and a small magnet is attached to the case of the instrument approximately 5 mm from the Hall device. As force is applied to the tablet, the shaft moves, causing the Hall device to move away from the magnet. This change in magnetic flux density is sensed by the Hall generator; its

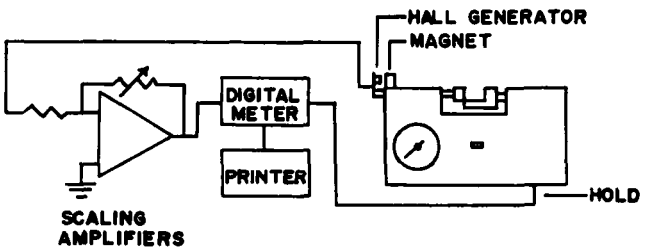

Figure 1—*Schematic diagram of instrument for digitizing tablet hardness.*

[1] Heberlein tester, Cherry-Burell, Park Ridge, Ill.
[2] Hall effect magnetic field sensor, model 63SS2-1, Micro Switch, Freeport, IL 61032