Independent of the substrate used, the RC and ADP:O ratios were similar in all three groups. This finding indicated that neither emetine nor malnutrition affected the coupling of oxidation to phosphorylation or the oxidative phosphorylation process, respectively.

The results from the liver mitochondrial studies also agreed with the findings of Appelt and Heim (6, 7). Since the respiration rates were lower only in the pair-fed control group in comparison to the normal control group, liver mitochondrial metabolism apparently was reduced by malnutrition. This effect was overcome in the emetine-treated rabbits.

Basically, it seemed that liver mitochondria were less susceptible to the effects of inanition than heart mitochondria. This result was consistent with observations in semistarved rats (17) and probably reflects the higher metabolic rates and energy requirement of the heart.

As with heart mitochondria, emetine treatment did not affect oxidative phosphorylation in liver mitochondria. Since no consistent effects on the RC ratio were observed in the pair-fed control group, mitochondrial coupling probably was not significantly affected by malnutrition.

In the present experiments, the heart mitochondria from emetine-treated rabbits appeared unaltered, except for a slight swelling of the cristae, when examined under the electron microscope. However, these observations appeared to reflect metabolic effects. Similar morphological findings also were noted by Hatt *et al.* (18) in rats chronically treated with emetine, but they differed from the results of Pearce *et al.* (9) and may reflect species differences. As seen by the treatment schedule used by Pearce's group, the dog may be more sensitive to the actions of emetine than the rat and rabbit.

Thus, the results of these experiments indicate that chronic therapeutic doses of emetine produced no direct detrimental effect on heart mitochondrial metabolism. Any effects observed were secondary to the inanition induced by chronic treatment. The different response noted in liver mitochondria probably reflected the different metabolic states of the heart and liver, as well as the unique metabolic response of the liver during semistarvation or starvation (19). Thus, it appears unlikely that metabolic damage to the myocardium will result from chronic therapeutic doses of emetine. This view agrees with the clinical observation that after therapeutic doses of emetine, most patients recover from cardiovascular side effects without any compromise in cardiac function.

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COMMUNICATIONS

General Equation for Assessing Drug Removal by Extracorporeal Devices

Keyphrases □ Pharmacokinetics—general equation for measurement of drug removal by extracorporeal devices □ Extracorporeal devices—general equation for measurement of drug removal □ Drug removal—by extracorporeal devices, general equation

To the Editor:

The efficiency of extracorporeal drug removal commonly is measured as dialysance or dialysis clearance. Such terms, however, do not correlate directly with the amount of drug removed by the device. Previous investigators (1, 2) proposed an alternative parameter, f, defined as the fraction of drug in the body at the start of extracorporeal drug removal (EDR) that is removed by the device. This fraction is the product of the fraction of total elimination that EDR represents and the fraction of drug lost by all elimination routes during EDR and is given by:

$$f = \frac{Cl_D}{Cl + Cl_D}\left[1 - e^{[-(Cl+Cl_D)/V]t}\right] \qquad \text{(Eq. 1)}$$

where Cl_D is the EDR clearance, Cl is the total body clearance in the absence of EDR, V is the apparent volume of distribution of the drug, and t is the duration of EDR.

Equation 1 assumes one-compartment pharmacokinetics; thus, for most drugs, it may yield inaccurate estimates of the fraction of drug removed by an extracorporeal device. An alternative general equation that can be used for drugs following single or multicompartment kinetics is developed in this communication.

Consider the mass balance equation:

$$X_S = X_D + X_{el} + X_f \qquad \text{(Eq. 2)}$$

where X_S and X_f are the amounts of drug in the body at the beginning and the end of EDR, respectively, and X_D and X_{el} are the amounts of drug eliminated by EDR and by the body during EDR, respectively. Equation 2 may be expressed as:

$$X_S = Cl_D AUC_1 + ClAUC_1 + ClAUC_2 \qquad \text{(Eq. 3)}$$

where AUC_1 is the area under the plasma concentration–time curve during EDR and AUC_2 is the area under the

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Table I—Comparison of Methods of Estimating the Fraction of Sotalol in the Body Removed by Hemodialysis [a]

Time of Dialysis, hr	AUC_1, mg/liter/hr	AUC_2, mg/liter/hr	f Eq. 1	f Eq. 4	f Eq. 5
1–7	5.87	6.77	0.17	0.26	0.26
12–18	1.75	3.67	0.17	0.20	0.20

[a] Pharmacokinetic parameters taken from Refs. 3 and 4; Cl = 140 ml/min, V = 136 liters, and Cl_D = 105 ml/min, with an intravenous bolus dose of 160 mg.

plasma concentration–time curve from the termination of EDR to infinity.

The fraction of drug in the body at the start of EDR that is removed by the device is given by:

$$f = \frac{X_D}{X_S} \qquad \text{(Eq. 4)}$$

which, from Eq. 3, may be expressed as:

$$f = \frac{Cl_D AUC_1}{(Cl + Cl_D)AUC_1 + ClAUC_2} \qquad \text{(Eq. 5)}$$

To test the validity of Eq. 5, plasma concentrations of sotalol, a β-adrenergic receptor blocking agent, were simulated by computer. Pharmacokinetic parameters describing the time course of this drug in the body were obtained from Sundquist *et al.* (3). Hemodialysis was started and terminated at 1 and 7 hr, respectively, following intravenous bolus administration. In a second simulation, dialysis was started and terminated at 12 and 18 hr following drug administration. A dialysis clearance, Cl_D, for sotalol of 105 ml/min was estimated from the study by Tjandramaga *et al.* (4). Areas under the plasma concentration–time curve were estimated using the trapezoidal rule.

By employing Eq. 4, f was determined directly using the simulated amounts in the plasma and tissue compartments at the beginning of dialysis, X_S, and the amount of drug removed by dialysis, X_D. The value of f obtained was compared with that obtained using Eqs. 1 and 5 (Table I).

Sotalol pharmacokinetics can be described by a two-compartment model with a distribution phase of ~10 hr. When dialysis is performed during the distribution phase of the drug, use of Eq. 1 underestimates the fraction of drug removed by dialysis. When dialysis is conducted in the postdistributive phase, the prediction of f using Eq. 1 improves but still underestimates this parameter. Regardless of the time of dialysis relative to drug administration, Eq. 5 accurately predicts the fraction of drug removed from the body.

Equation 5 provides a valid means of determining the fraction of drug removed by EDR. It is more general than Eq. 1 in that it can be applied to drugs following multicompartment pharmacokinetics regardless of the time of EDR relative to drug administration. The clearance values are easily obtained. Proper use of the equation requires that the final plasma sample be obtained during the terminal log-linear phase of the plasma drug concentration curve and that the slope of this linear phase be determined to estimate AUC_2 accurately.

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Novel Source of Ubiquitous Phthalates as Analytical Contaminant

Keyphrases □ Plasticizers—phthalate, analytical contaminant □ Mass spectrometry—detection of phthalate esters by selected-ion monitoring □ Phthalates—interference with oxprenolol assay using GLC with electron-capture detection □ Contaminants—phthalates, interference in drug assays using electron-capture detection

To the Editor:

The ubiquitous distribution of the phthalate ester plasticizers in the environment is well known, and they are frequently encountered in samples processed in biomedical laboratories. Although the analyst can often identify phthalate plasticizers in biological samples, it is not always clear whether the plasticizer is a genuine contaminant in the specimen or an analytical artifact (1). Phthalates are readily leached into blood stored in plastic containers (2), and collecting blood specimens with evacuated tubes (3) or some plastic syringes (1) can result in contamination with phthalates or other plasticizers.

In addition to their ubiquity, the phthalates manifest two other frustrating properties for the analyst. First, the range of phthalate esters used commercially ensures that a phthalate will cochromatograph with many analytes of interest such as barbiturates (4), disopyramide (5), and long-chain fatty acids (6). Second, although the phthalate esters contain no halogen atoms, they show good response factors to the electron-capture detector (7), which ensures that even nanogram quantities may interfere in trace level determinations of some compounds.

The range of reported sources of phthalates as analytical contaminants is impressive, but we recently encountered a novel and unexpected source that could be of importance to analysts using electron-capture detection for trace level assay of drugs.

To carry out low dose bioavailability studies with oxprenolol, a sensitive assay for this β-blocking drug in plasma was required. An assay by GLC with electron-capture detection, using heptafluorobutyryl derivatives of oxprenolol and the internal standard (metoprolol), was investigated. However, assay blanks invariably contained a spurious peak with a retention time almost equivalent to that of derivatized oxprenolol. A phthalate plasticizer was suspected, so meticulous care was taken to ensure that no plastic materials came in contact with any glassware, reagents, or specimens used. The contaminant persisted, and one of the offending blanks was subjected to GLC–mass spectrometric analysis to confirm the presence of the suspected phthalate. No confirmation could be established

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