Serum Creatinine and Drug Half-Lives in Renal Failure

To the Editor.—Serum creatinine concentrations as well as creatinine clearances have been used as a basis for adjusting the dosage regimen of certain drugs in patients with impaired renal function. Although mathematical relationships have been developed by Dettli et al[1] relating the first-order elimination of a drug in renal failure to creatinine clearance, little has been done to relate the half-life or elimination rate of a drug to steady-state serum creatinine levels. Where serum creatinine has been employed to modify dosage regimens in patients with renal failure, it appears that the half-life of a drug was empirically assumed to be related directly to the steady-state serum creatinine concentration.[2-4]

It can be demonstrated mathematically that creatinine clearance is inversely proportional to the steady-state serum creatinine concentration where the proportionality constant is the endogenous production rate of creatinine. The validity of this relationship can be illustrated by plotting creatinine clearance vs 1/serum creatinine. We have made such plots using data from the literature,[2-5] and have obtained slopes ranging from 0.8 to 1.17 mg/min, which are in good agreement with reported endogenous creatinine production rates.[6] Since creatinine clearance is inversely proportional to the half-life of a drug,[1] as well as to serum creatinine levels, a double reciprocal relationship should exist between half-life, ($t_{1/2}$) and steady-state serum creatinine concentration, (CSS), such that

$$\frac{1}{t_{1/2}} = a \cdot \frac{1}{CSS} + b$$

where "a" is a constant associated with the endogenous creatinine production rate and the degree of renal excretion of a drug, and "b" is related to the degree of metabolism of a drug.[1]

For drugs eliminated totally by renal excretion, the term "b" is zero, and the half-life can be directly related to the steady state serum creatinine concentration, ie, $t_{1/2} = CSS/a$. Therefore, adjustments in dosage regimens for drugs such as kanamycin and gentamicin which are essentially totally eliminated by the kidney are valid if a linear relationship is assumed between half-life and serum creatinine. However, if a drug is metabolized to any significant extent, this simplification is not valid and adjustments in dosage regimens should be based on the relationship between half-life and serum creatinine, as in the equation.

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The Coronary Drug Project

To the Editor.—The directors of the Coronary Drug Project (220:996, 1972) should be congratulated for including thyroid in an attempt to delay atherosclerosis. For more than 75 years evidence has been mounting that (1) thyroid deficiency promotes both experimental and clinical atherosclerosis, and (2) desiccated thyroid therapy is safe and effective in delaying vascular accidents in patients with advanced arterial damage.[1]

By the same token, the directors should be censored for selecting dextrothyroxine sodium, a synthetic preparation of variable activity, which has been listed as contraindicated in coronary disease by the *Physicians Desk Reference.* Undoubtedly, they were misled by statements that this analogue has less metabolic activity than the natural hormone. Per unit of weight, this is true, but effective dosages of each compound reveal that desiccated thyroid or levothyroxine sodium is superior to dextrothyroxine for the reduction of serum lipids. Best and Duncan[2] found that in the human, 4 mg of dextrothyroxine sodium was equivalent to 0.3 mg of levothyroxine sodium. The use of 6 mg of dextrothyroxine sodium by the Coronary Drug Project represented the calorigenic equivalent of 0.45 mg of levothyroxine sodium or 4.5 grains of desiccated thyroid. Since 1925 it has been repeatedly demonstrated that such dosages may be fatal in patients with coronary disease.

The confusion over the proper dosage of thyroid hormone as a prophylactic in coronary disease has been explained in a recent book.[3] In a 20-year study of more than 1,500 patients maintained with physiological doses of thyroid hormone, new cases of coronary disease were rare compared to the incidence found in the Framingham Study. Patients were matched as to age, sex, and the presence of hypertension or hypercholesterolemia, or both.

In a preliminary report,[4] a maximum of two grains of desiccated thyroid was found safe and effective when given to patients surviving a previous myocardial infarction. Unpublished observations on more than 40 similar patients indicate that institutions equipped for double-blind studies should be investigating this approach to the coronary disease problem.

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To the Editor.—The Coronary Drug Project's report (220:996, 1972) of long-term therapy with dextrothyroxine sodium refers to calorigenic effects due to levothyroxine sodium contamination as possible explanation for the adverse effects. This observation has led to the discontinuation of the drug regimen in the project.

We have assayed several samples of the dextrothyroxine commercially available in the United States by a modification of a very sensitive method[1] that allows detection of levothyroxine contamination as low as 0.1%. The dextrothyroxine preparations we tested were found to contain 0.8% to 1.0% of levothyroxine. Daily doses of 6 mg of dextrothyroxine sodium thus contain up to 60μg levothyroxine sodium, an amount that may very well exert calorigenic effects significant in regard to aggravation of coronary heart disease.

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