LETTERS TO THE EDITOR

Re: Age and Sex Differences in Thyroid Function Tests

The study of age- and sex-dependent changes in thyroid function tests by Lipson et al. (*1*), which appeared in the November issue of the *Journal*, served to clarify and unify reports by other workers that suggested definite changes in various thyroid function values with varying age and sex. Unlike most other studies, which were primarily concerned with only one or two thyroid function parameters, this study reports the results of the five most popular thyroid function tests (T_4-RIA, T_3 uptake, free thyroxine index, T_3-RIA, TSH) as well as rT_3-RIA determinations in a single large group of patients. Lipson's results suggest that males maintain stable values of T_4, T_3U, FT_4I and TSH throughout adult life, but experience modest decreases in T_3 and rT_3 after age 60. Females, on the other hand, appear to have changes in T_3U and TSH, which increase with advancing age, and changes in T_4, T_3, and rT_3, which decrease with age. The FT_4I remains stable despite advancing age.

The authors offer several explanations for these age and sex differences, the most likely of which depends upon the effect of estrogen levels on the titer of thyroxine-binding proteins. Age-related diminutions in circulating estrogens lead to decreased levels of thyroxine-binding proteins and total thyroxine. Lipson et al. have some diffculty in explaining TSH increases in older women. It seems to me that premenopausal women, because of higher thyroxine-binding protein levels and concomitantly higher total T_4 levels, may have more effective feedback inhibition of TSH secretion than their age-cohort males, who have lower T_4 titers; the data in Lipson's study confirm this interpretation. As estrogen secretion declines in older women, thyroxine-binding protein levels and T_4 titers drop, creating a relative T_4-deficient milieu for the pituitary and hypothalamus, which respond with increased TSH secretion and enhanced TSH responsiveness (*2*). The aging thyroid may be incapable of reacting to this subtle stimulus, as evidenced by the age-related drop in T_3 and rT_3 levels in both sexes. A permanent increase in TSH levels may ensue. This hypothesis is dependent on the assumption that protein-bound thyroxine, as well as free thyroxine, may have suppressive activity at the pituitary and/or hypothalamic levels. Our current knowledge is not sufficient to preclude this possibility.

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REFERENCES

1. LIPSON A, NICKOLOFF EL, HSU TH, et al: A study of age-dependent changes in thyroid function tests in adults. *J Nucl Med* 20:1124-1130, 1979
2. AZIZI F, VAGENAKIS AG, PORTNAY GI, et al: Pituitary-thyroid responsiveness to intramuscular thyrotropin-releasing hormone based on analyses of serum thyroxine, tri-iodothyronine and thyrotropin concentrations. *N Engl J Med* 292: 273-277, 1975

Reply

At present our observed age-related increase in TSH in women over age 60 remains unexplained. Although a small decline in total T_4 occurred in older women, it is unlikely that age is the explanation, since a decrease in free T_4 (as approximated by free T_4 index) was not demonstrated, and it is unlikely that bound thyroid hormone alters the hypothalamic-pituitary-thyroid axis.

In some unpublished work, we examined the free T_3 index (T_3 uptake ratio × total T_3 concentration, an approximation of the free T_3 concentration) in this group of subjects and found similar small declines in both older men and women. It is believed that the free thyroid hormones (T_4 and T_3) are the main modulators of the hypothalamic-pituitary-thyroid axis. Therefore, it is possible that older women are more responsive than older men to small changes in free T_3 concentration and demonstrate a small increase in TSH concentration in response to this change. This would be in keeping with the observed TSH hyporesponsiveness of older men to TRH injections (*1,2*).

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REFERENCES

1. SNYDER PJ, UTIGER RD: Thyrotropin response to thyrotropin releasing hormone in normal females over forty. *J Clin Endocrinol Metab* 34: 1096-1098, 1972
2. AZIZI F, VAGENAKIS AG, PORTNAY GI, et al: Pituitary-thyroid responsiveness to intramuscular thyrotropin-releasing hormone based on analyses of serum thyroxine, tri-iodothyronine, and thyrotropin concentration. *N Engl J Med* 292: 273-277, 1975

Uptake of Bone Seekers as a Function of Blood Flow in the Rat

In the December issue of this *Journal*, N. David Charkes and his colleagues (*1*) showed in the dog that increments of tibial blood flow up to four times that of normal produced only minimal augmentation of Tc-99m MDP uptake at 75 min. We have observed a similar behavior of Tc-99m pyrophosphate and Ca-45 in the femur and tibia of the intact rat (*2*). The bone-blood flow was

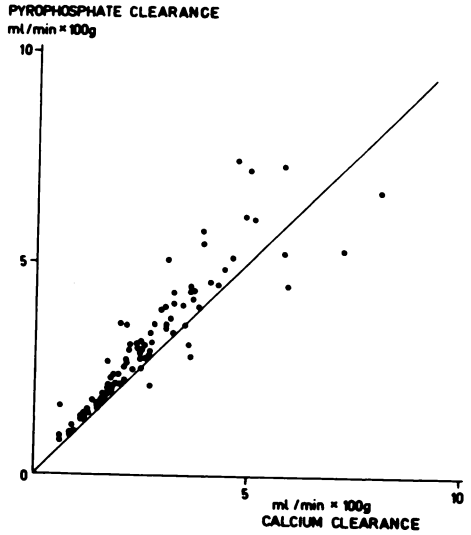

FIG. 1. Relationship between 10-min Tc-99m pyrophosphate clearance and 10-min Ca-45 bone clearance. Identity line is shown.

modified by heating and cooling the hind limbs of the animal. Osseous blood flow was measured by the arteriolar trapping of labeled microspheres of 15 μm diameter injected into the left ventricle. The plasma clearances of Ca-45 and Tc-99m pyrophosphate

$$\left(\frac{\text{bone activity in Ca-45 or Tc-99m}}{\text{mean activity in Ca-45 or Tc-99m/ml plasma}} \times \text{time since injection}\right)$$

were measured over 10 min and 1 hr intervals. At 10 min, Tc-99m pyrophosphate clearance by the femur and the tibia was significantly higher than the calcium clearance (Fig. 1). At 60 min, both clearances were similar. Ten-minute and 1-hr clearances showed the same basic relationship with bone-blood flow (Fig. 2): the extraction ratio for Tc-99m and Ca-45 dropped as flow increased. Our conclusion was that initial blood clearances of bone seekers should not be used to measure the increases in bone blood flow over the values at rest.

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REFERENCES

1. SAGAR VV, PICCONE JM, CHARKES ND: Studies of skeletal tracer kinetics. III. Tc-99m(Sn)methylenediphosphonate uptake in the canine tibia as a function of blood flow. *J Nucl Med* 20: 1257-1261, 1979
2. SCHOUTENS A, BERGMANN P, VERHAS M: Bone blood flow measured by ^{85}Sr microspheres and bone seeker clearances in the rat. *Am J Physiol* 236(1): H1-H6, 1979

Re: Studies of Skeletal Tracer Kinetics. III. Tc-99m(Sn)Methylenediphosphonate Uptake as a Function of Blood Flow

I admired the research approach taken by Drs. Sagar, Piccone, and Charkes (*1*) in their attempt to determine the exact relationship between bone blood flow and Tc-99m MDP uptake within canine tibia. Their postulate of a rate-limiting step in the process of radiopharmaceutical transfer into bone appears to be consistent with clinical findings. However, their analysis of the data as represented in Figs. 3 and 4 does not satisfy all of the requirements of a statistical regression.

Residual error, the deviation between an observation and its predicted value, must be assumed to be normally and independently distributed before a test of significance is performed. If one does a residual analysis of their data, it can be observed that there are more observations appearing above the predicted curve than below and that the sign and magnitude of these errors is directly related to the input variable, relative blood flow or perfusion. From this analysis, it cannot be proven that the data fit the predicted model.

In addition, in order to prove that the clearance curve does indeed have "a sharp bend," one should have a higher sampling rate at the interval that has the higher rate of change. In the present

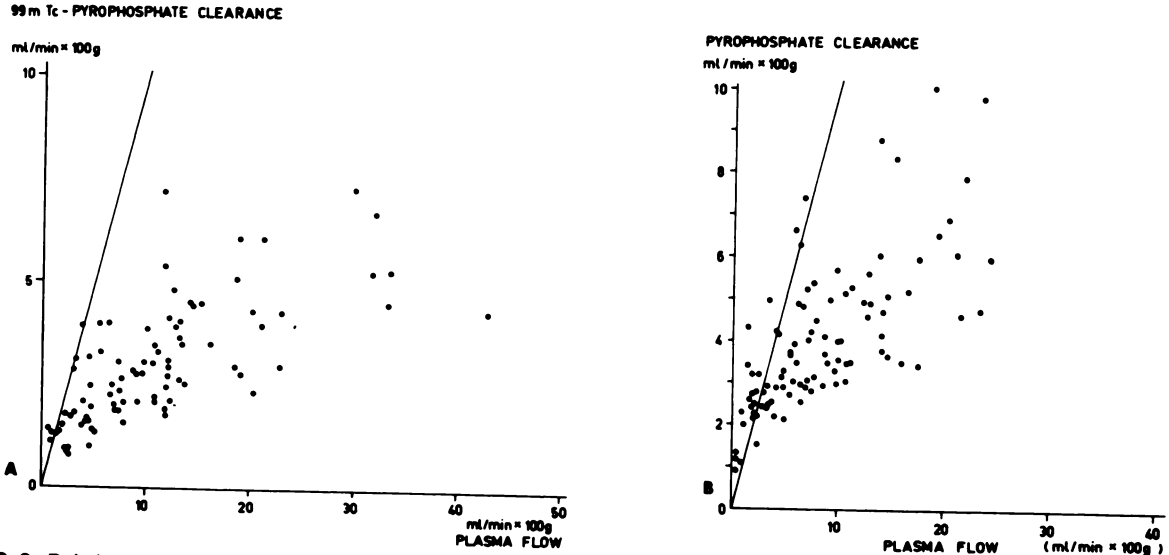

FIG. 2. Relationship between the 10-min (A) (ref *2*) and 1-hr (B) Tc-99m pyrophosphate bone clearance and the bone plasma flow—femur and tibia.