effects of amiodarone on thyroid metabolism. The initial assessment of amiodarone-induced thyrotoxicosis (AiT) showed high values of serum T_3, which is *not* an effect of amiodarone. Our experience agrees with that of Burger et al. Amiodarone-treated patients without thyrotoxicosis should have normal or low serum T_3 (*1*). In the patients described, thyrotoxicosis was clinically obvious; clinical details were not given because they were trivial. We have never observed such high T_3 levels in patients under amiodarone but without clinical symptoms of thyrotoxicosis. Thus, we confirm that these patients were clinically and biologically thyrotoxic.

We agree that the syndrome we describe differs from that observed in endemic goiter areas, where thyrotoxicosis could be unmasked or exacerbated by iodine supplementation in patients with underlying thyroid abnormalities such as nodularity and/or autonomy. In our patients with AiT, the 24-hr I-131 thyroid uptake was found to be very low and responsive to exogenous TSH (*2*). This is not the case of Graves' disease with iodine excess. In our experience the mean I-131 24-hr uptake in Graves' disease with iodine excess was 20% (limits: 5–50%) and remained unchanged under exogenous TSH. In AiT the serum T_3 returned to normal values in both treated and untreated patients within a few months. After cure, no thyroid abnormalities—whether clinical, scintigraphic, or biological—remain detectable.

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Re: Salivary Thyroxine as an Estimate of Free Thyroxine

In their study of the potential usefulness of salivary thyroxine (T_4) as an indicator of serum free T_4, Elson et al. (*1*) found salivary levels about ten times the serum free hormone, with no correlation between the two. Salivary T_4 and albumin levels, however, were significantly correlated. The authors proposed that plasma proteins may cross the salivary glands and carry bound T_4 into the saliva, and they drew the general conclusion that salivary levels of drugs and hormones may be strongly affected by protein binding in saliva, so that caution must be exercised in using salivary levels as estimates of circulating free levels.

Elson et al. appear not to have considered the most likely explanation for their observations, and we wish to point this out in order to correct any misleading impression of the reliability and usefulness of salivary assays. The mechanisms whereby materials from plasma may appear in saliva are well recognized (*2*). All evidence suggests that plasma proteins are much too big to cross the salivary membranes, and the reason for their presence in variable, trace amounts in saliva is contamination with blood (from minor abrasions in the mouth) or gingival fluid.

For highly protein-bound plasma constituents—such as T_4 that has a total-to-free ratio of about 5,000:1—even trace contamination with saliva may easily outweigh any contribution due to passive diffusion of the free fraction from plasma across the salivary glands (*2*). Relatively high and variable levels of salivary T_4 (*1*,*2*) are best accounted for in this way. The observed correlation (*1*) between salivary T_4 and albumin is consistent with their origin from contaminating plasma.

Thus, the lack of clinical value of salivary T_4 levels can be understood (and predicted) on the basis of known principles: these include the rule (*2*) that the concentration in saliva of any material that (because of its size, charge, or plasma protein binding) has an expected plasma-to-saliva ratio of more than 1,000:1 is unlikely to be useful because of the problem of trace contamination by plasma or gingival fluid. This is the accepted reasoning underlying the deduction (*1*) that the use of salivary levels as indices of free levels in circulating plasma may well be limited to molecules that are not strongly bound to plasma proteins. Protein binding in saliva is not, in general, a significant consideration.

In appropriate circumstances, salivary assays will give a reliable indication of plasma free levels. Such is the case for cortisol, as shown by Elson et al. (*1*) and our own studies (*3*), and for a wide range of other steroids (*2*,*4*) and drugs (*5*).

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Reply

We thank Drs. Al-Ansari et al. for their interest in our report on salivary thyroxine (*1*). We certainly agree that salivary levels of hormones may be strongly affected by plasma proteins in the saliva. While we considered gingival fluid and blood as possible sources of plasma proteins, we doubt that either is a major source of salivary albumin. We discounted their significance for the following reasons:

1. The displacement curve generated by diluting serum to the appropriate range for analysis is much flatter than the standard curve or the identical solution of saliva.

2. Both TBG and TBPA have higher affinity for T_4 than albumin, and interfere with the antiserum when binding inhibitors are absent.

3. In the subject who was sampled sequentially through the day, spikes of salivary T_4 were observed just before meals. Salivary flow was increased at those times, but we find it difficult to imagine increased gingival flow in anticipation of a meal.

The primary conclusion of our report was that salivary levels of drugs or hormones may be strongly affected by salivary proteins, and caution must be exercised if salivary levels are used to estimate

circulating free levels. In a recent publication, Vining et al. reached the same conclusion, although their T_4 assay lacked the sensitivity to measure salivary T_4 accurately (*2*).

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Re: The Derivation of the Gamma-Variate Relationship for Tracer Dilution Curves

Mr. Davenport should be commended for his elegant derivation of the gamma-variate function for indicator dilution curves (*1*). I have, however, one minor question: Pursuant to Eq. 18, the statement is made, "Since the total amount of tracer injected at the beginning of the vessel is assumed to be unity, we must have

$$\int_0^\infty C(\alpha, \beta, t)dt = 1 \ldots$$

However, since the quantity $C(\alpha, \beta, t)$ is a concentration, should not the integral extend over a volume that in turn is evaluated at $t = 0$? Perhaps the author should have said that, by convention, the area under the gamma variate is taken to be unity.

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Reply

Dr. Harpen is correct in pointing out that Eq. (18) refers to a concentration rather than an amount. There are a couple of ways of resolving this discrepancy. One is to stipulate that the area under the curve be unity, as Dr. Harpen suggests. Another would be to multiply by the volume of distribution, V, and set the product equal to unity. Since the initial amount of tracer injected at $t = 0$ is diluted in the volume, V, of a theoretical mixing chamber, the result would be the same.

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Re: New Perspectives in Localizing Enlarged Parathyroids by Technetium-Thallium Subtraction Scan

We read with great interest the recent report by Ferlin et al. (*1*) on imaging parathyroid adenomas by combined technetium and thallium subtraction scans. The relatively noninvasive nature of the combined scanning technique, with its high success rate, offers an attractive imaging modality in these patients. Previous imaging modalities—including barium esophagrams, thyroid angiography, and venous sampling for parathormone levels—have all had varying success rates in locating parathyroid adenomas. Recently, higher success rates have been achieved with high-resolution TCT scanning and high-resolution ultrasound scanning. Intravenous digital subtraction angiography (i.v. DSA) may also prove to be a useful adjunct in parathyroid imaging. Levy et al. reported i.v. DSA to be positive in six of seven patients (*2*). Patient selection may have been responsible for this high success rate. We have evaluated a prospective, consecutive series of 13 patients with parathyroid adenomas, and i.v. DSA identified only four.

In view of these difficulties in imaging parathyroid adenomas, Ferlin's results seem encouraging. We utilized their combined scanning technique to locate correctly a 4-g parathyroid adenoma in a patient with persistent elevated calcium and PTH levels (Fig. 1). However, in reviewing the Methods and Materials section of their paper, we noted that their patients were first given 1 mCi of pertechnetate and then were given thallium. From a purely tech-

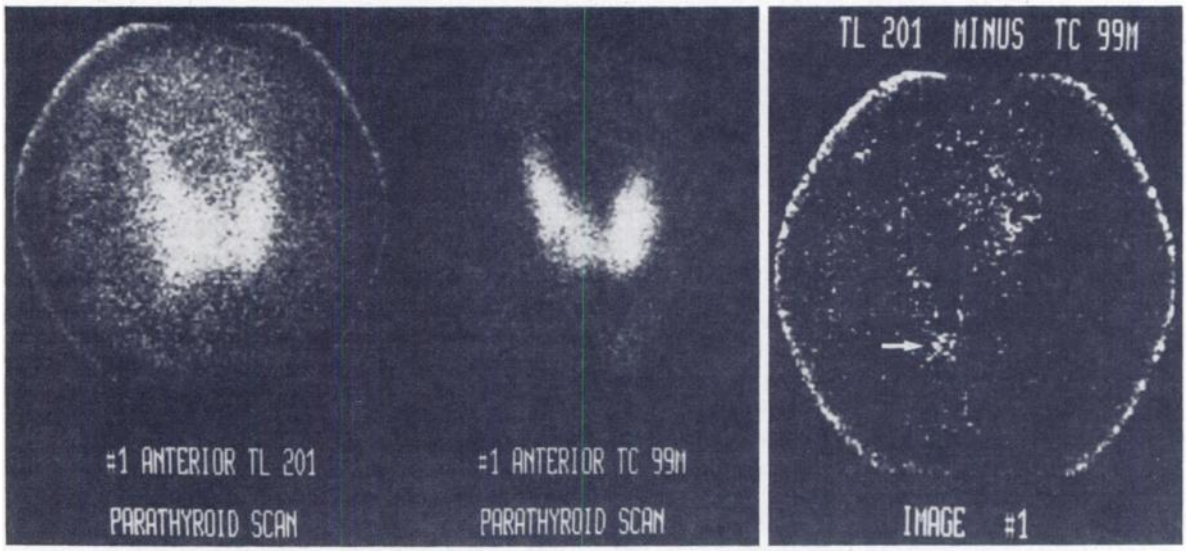

FIG. 1. Thallium pinhole thyroid scan shows increased uptake in right lower pole of thyroid (left). Tc-99m pertechnetate scan shows small defect in same area (center). Subtraction image confirms presence of thallium-avid nodule at lower pole of right lobe of thyroid (right). Surgery confirmed 1.5-cm parathyroid adenoma in this area.