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Reply

We must agree that our results differ slightly from those of Prof. Jonckheer. It is our experience (*1*,*2*) that if patients show no antithyroid antibodies, and remain euthyroid under amidarone, only half of them will show thyroid iodine contents that are above normal. On the other hand, 80% of the patients who become hyperthyroid under amiodarone therapy have higher than normal thyroid iodine, the mean content being 2.8 times normal (*2*). We look forward to reviewing Prof. Jonckheer's data upon publication and comparing it with ours.

In Graves' disease, the thyroid iodine content was normal in 58% of our cases, high in 20%, and low in only 22%, which is at variance with Jonckheer's data (*3*). However, we agree that our statement should have been more precise. Furthermore the total iodine content in most iodine-induced thyrotoxicosis is high, whereas most patients with Graves' disease have a normal *or low* thyroid iodine content (*1*). In fact, what we wished to emphasize is the lack of elevation of the thyroid iodine content among patients with Graves' disease. This stresses the role of x-ray fluorescence in discussions of the hypothesized mechanism of iodine-induced hyperthyroidism.

We agree that patients with antithyroid antibodies, when treated with amiodarone, should be followed up very closely. We have shown recently (*4*) that in one third of these patients with thyroid antibodies, iodine supplementation (500 μg/day) progressively increased the thyroid iodine content, up to very high levels in some cases; nevertheless, none of these patients became hyperthyroid. In patients with high cardiovascular risk, measurements of the thyroid iodine content during amiodarone therapy could prove to be useful in the prediction of amiodarone-induced hyperthyroidism.

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Re: Thyroid Iodine Content Measured by X-Ray Fluorescence in Amiodarone-Induced Thyrotoxicosis: Concise Communication

The report of Léger et al. (*1*) in the July issue of the *Journal* is interesting in that the syndrome described differs markedly from iodine-induced thyrotoxicosis occurring in other parts of the world. I would make the following points:

1. The incidence in this series appears to be much greater than the 80 per 100,000 population that is usual in the Iodbasedow syndrome (*2*).
2. Decreased radioiodine uptake was certainly not a feature in our series.
3. In the great majority of cases from other centers, once thyrotoxicosis has developed it continues despite iodine withdrawal.
4. Response to antithyroid drugs was a feature in our patients.

It is noteworthy that the amount of iodine consumed by the French patients was much higher than that required in others, and that the "hardness" of their glands was so obvious. When describing the Iodbasedow phenomenon in Tasmania, we found that clinical assessment was a mandatory part of our investigation, and this is curiously lacking in the article under discussion. Johns et al. (*3*) describe several patients who were clinically and biochemically euthyroid before amiodarone, but who developed biochemical but no clinical evidence of hyperthyroidism when taking this drug. Clinical thyrotoxicosis did not develop in these patients when the drug was continued.

I suspect that Léger et al. are describing the effect of excess iodine plus the peripheral and central effects of amiodarone, namely the combined effect of reduced T_4 to T_3 production with increased T_3 and increased TSH response to TRH, producing increased T_3 and T_4 output (*4*).

This is not Iodbasedow or iodine-induced thyrotoxicosis as described by Kocher (*5*), others, and ourselves.

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Reply

We were surprised at Dr. Connolly's suspicion that we have confused amiodarone-induced thyrotoxicosis with the known other

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