mous thyroid nodule (*5*) showed no therapy failure one year after treatment (i.e., no residual hyperthyroidism and no recurrence within 9 yr) against 13.6% and 10% [(*1*), all autonomous thyroid nodules and decompensated autonomous thyroid nodules, respectively]. The incidence of hypothyroidism, due in part to spontaneous involution of thyroid function, even in the absence of therapy (*5*), was comparable under both dosage regimens: 11.9% in Berne against 9.6% in Paris [both 75 mo after treatment; calculation based on an annual cumulative hypothyroidism rate of 1.9% in Berne, see Table 4 in Ref. *5*]. Moreover, no long-term sequelae, such as bone marrow depression, were registered in the Bernese patients up to 9 yr after treatment.

Thus, the authors' objective, "... rapid elimination of hyperthyroidism is desirable ...," validated by their patient survival data, was met more effectively with our higher dose [or with surgery (*5*)]. The statement "... hypothyroidism is a lesser evil compared to failure of treatment ..." is clearly also valid for a higher dose, e.g., 300 Gy, that leads to similar rates of hypothyroidism and cures hyperthyroidism by eradicating its cause (*5*).

What is the physiological justification for uniformly treating autonomous thyroid nodules with a dose of 80 Gy independently of a suppressed or nonsuppressed TSH? Why treat euthyroid autonomous thyroid nodule patients by therapeutic doses of radioiodine without protecting the perinodular tissue by suppressive doses of thyroid hormone?

The life-table estimates for death were 22% at 75 mo (*1*). In Berne, with an expected death rate of 17.5% of the overall age-related population, the estimates for the patients were 20% after 9 yr [radioiodine and surgery together (*5*)]. The average age of the investigated autonomous thyroid nodule patient population was slightly higher in Paris than in Berne (64.5 versus 61.5 yr), as was the age of the patients who died [74 ± 4 yr (*1*), versus 62 ± 10 yr (*5*)]. The authors deduce that "... hyperthyroidism and its related complications are responsible for this fatal outcome." To support this statement, some additional information is missing, such as the mortality rate of a control population, matched for age and sex and the number of residual "supraventricular arythmias ... and left ventricular hypertropies" after radioiodine therapy as causes of death.

The authors treated "... single hot nodules ..." only, but in some cases postulate a transition into multifocal functional autonomy under therapeutic doses of $^{131}$I: "... autonomous millimetric nodules ... often imaged with ... and sonography. ..." Doesn't sonography image and measure morphologic changes and no more? A detailed case report would have been helpful, particularly because we (*6*) and others (*7*) have been unable to substantiate a spontaneous evolution from an autonomous thyroid nodule to multifocal functional autonomy, despite interesting hypotheses based on in vitro experimentation concerning such a development.

Antithyroid antibodies were determined and related to some unclear causative effect on the late outcome after radioiodine therapy, but the titers were not documented. Did the authors register secondary basedowification?

The final remark in the abstract which recommends administering amounts of radioactivity as fixed doses does not conform to standard terminology in nuclear medicine and could thus be misunderstood. Moreover, the systematic, individual calculation of the administered activity is a minimal but very useful expense in this context.

Treatment of autonomous thyroid nodule with radioiodine is reliable, successful and rather predictable in its outcome if appropriate precautions are taken (*4,5*). The "recommendations for standard protocols on therapy with radioiodine in nonmalignant diseases of the thyroid" (*4*), which "aim to achieve a general consistency within the nuclear medicine community," were published in 1991. These guidelines, which present adequate definitions and precise dose recommendations, represent a consensus reached after study of many long-term experiences in Continental Europe. These guidelines may not have been followed from 1979 to 1989 but, hopefully, have been applied since.

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**REPLY:** As usual, when $^{131}$I therapy is used for thyrotoxicosis, the question is to know whether there is a best intended absorbed dose and, correlatively, a best dosing scheme for activity calculation.

The best intended absorbed dose level remains controversial because the success of treatment, its cost, convenience for the patient and the limitation of whole-body irradiation must all be considered at the same time. In such a context, it is helpful to dispose of objective dosimetric criteria. Our intended absorbed dose of 80 Gy is indeed low, but was previously used by both us and others with acceptable clinical success rates, especially in a subset of patients diagnosed earlier at younger ages and who presented with low toxic forms (*1,2*). We recommended the higher intended absorbed dose (130–150 Gy) for other patients. An intended absorbed dose of 300 Gy or more will obviously cure patients but at the cost of higher individual whole-body irradiation. In addition, a higher intended absorbed dose mainly shortens the time to cure without excessively affecting the percentage of patients cured at one year. Not only does the intended absorbed dose level reflect a medical strategy, which is partly unavoidable due to local habits and legal constraints, but it may be adjusted according to the patients. Indeed, there is no firm evidence that the intrinsic radiosensitivity of AFTN is comparable among individuals. If such evidence were to exist, it is likely that it would be erroneous since AFTN correspond in fact to miscellaneous mutations of the TSH receptor or of the stimulatory Gs protein (*3,4*). Variations in the stable intrathyroidal iodine stores (*5*), histologic variations, the presence of necrosis and of factors affecting the dosimetry at the multicellular level are numerous and not well apprehended. Finally, comparisons between series are difficult, if not impossible, because basic dosimetric data are often missing, and because pathologic definitions vary from one center to another. What is called nonimmunogenic nodular hyperthyroidism corresponds to a variety of diseases ranging from the single toxic AFTN to a series of multinodular toxic goiters which may require higher intended absorbed dose. For example, patients with toxic adenoma may also have multiple nodules, some of which may also be cold (*6*), which is an exclusion criterion in our study. Finally, the physicians in the Berlin task group meeting who recommended higher intended absorbed dose were mainly from Eastern and Central Europe, where single toxic AFTN may be less frequent than multifocal autonomy (*7*).

Until now, little has been done to compare the efficacy of a simple fixed dose to more sophisticated dosing schemes. We clearly showed that the more sophisticated the dosing scheme, the less the resulting coefficient of variation of absorbed dose to the target: 45% with the fixed dose, about 25% with the uptake-based methods and only 13% with Marinelli method.

As a consequence, sophisticated methods are mainly means of reducing the required individual therapeutic activity. A more interesting concept is that the dose distribution conditions the clinical outcome of AFTN patients far more than the dosing scheme. You probably misred Table 3, since we almost reached our intended absorbed dose of 80 Gy using the Marinelli method (mean 80.5 Gy to the whole thyroid, 72 Gy to the AFTN) in patients with no extranodular activity (no-ENA), although underdosing occurred in patients with ENA. At any rate, the mean absorbed dose to the extranodular lobe (8.5 Gy) was far from insignificant in no-ENA patients, and would have been more than 3-fold higher using 300 Gy, a dose level constituting a high risk for secondary hypothyroidism. ENA patients correspond to two subgroups of patients. Those with "compensated AFTN" can successfully be cured with a low intended absorbed dose and hence with low activities. Adjuvant thyroxine therapy may limit secondary hypothyroidism, as suggested in this paper, although we have no experience of this therapeutic modality. ENA patients with "decompensated AFTN" were shown to have unpalpable multifocal autonomy, because significant focal uptake and imaging could be evidenced in the non-AFTN lobe. This is highly consistent with the fact that hypothyroidism may not develop in such patients, despite a mean dose of 49 Gy delivered. Indeed, the nonuniformity of dose distribution will spare healthy tissue from the beta irradiation. Ultrasonography may depict millimetric nodules in areas showing evidence of scintigraphic autonomy (Fig. 1), although it is true that autoradiographic proof is mandatory for definite conclusions.

Our mortality estimates are very similar to those observed in Berne and are clearly higher than those of the matched control population in Paris (13.5% expected versus 22% in AFTN patients, $p<0.01$). As both our studies are retrospective analyses, however, the excess mortality may reflect a bias in the choice of the therapy because more severely ill patients are usually referred for iodine and not for surgery. Hyperthyroidism, which may cause cardiac complications, the main cause of death in AFTN patients, is more likely responsible for the fatal outcome than $^{131}I$, because most of the patients died once cured and long after the therapy. Although large epidemiological studies serve to strengthen this point of view, there is still no definitive argument in favor of propylactic therapy for low toxic forms of AFTN.

The prevalence of antithyroid antibodies in patients with thyroid autonomy is low in Paris: antimicrosomial antibodies (ATPO not available at that time) were undetectable in 90% of patients, at the threshold (1/400) in 6% or slightly elevated in 4%. Finally the incidence of autoimmune thyroiditis after $^{131}I$ remains, at first glance, extremely low in this group of patients.

As epidemiological studies, the clinical presentation, and the molecular dissection show that thyroid autonomy is a moving spectrum of diseases, we think that a "best dose of 300 Gy" cannot be considered as a universal gold standard. We agree, and had suggested that the individual calculation of the activity, which can be done using early uptake values, remains interesting, mainly for radioprotection which is increasingly a public health concern.

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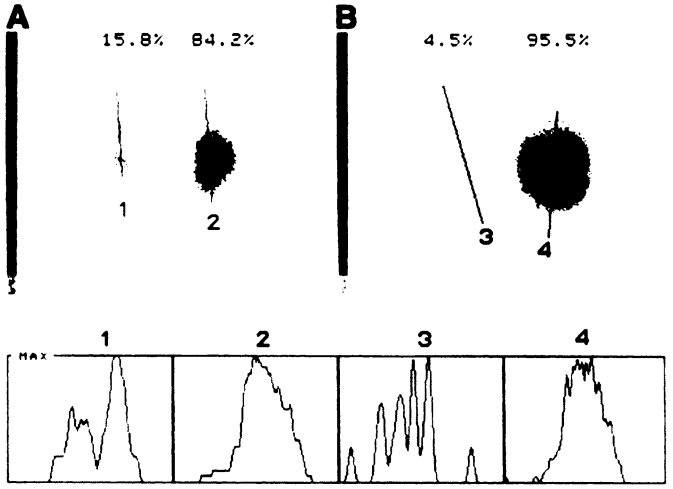


**FIGURE 1.** Two patients with left toxic AFTN (TSH<0.03 μU/ml) corresponding to a single palpable thyroid nodule. Patient A had evidence of $^{123}I$ activity in the right lobe which corresponds to at least two foci of autonomy, clearly visible on the radioactive profile 1. Ultrasonography depicted 4 millimetric nodules ranging from 3 to 7 mm. Patient B had a typical toxic adenoma with no significant activity in the right lobe (profile 3) which is homogeneous using US. Relative lobar counts are presented at the top of each lobe. Profile curves (P) are smoothed and normalized to their maximum (P1:8, P2:25, P3:3, P4:26).

## Is Renography Suitable for Deconvolution Analysis?

**TO THE EDITOR:** The application of deconvolution analysis to a renogram is particularly attractive, as it theoretically allows one to obtain the spectrum of intrarenal transit time (*1*). Many reports have been published which assess the clinical value of transit parameters obtained by deconvolution, as well as reports describing methods for performing the deconvolution (*1–2*). Few authors, however, have addressed the central issue: whether or not a renogram is suitable for deconvolution analysis. Two conditions should be respected for deconvolution analysis to work: linearity and stationarity (*1*). By applying deconvolution to the renogram, we assume that, in the kidney, these conditions are fulfilled. During the last few years, however, evidence has accumulated which raises doubt about the validity of these assumptions.

- For some radiotracers commonly used for renography, the renal extraction rate may vary with time. This has been repeatedly demonstrated for iodine-labeled hippuran (*3,4*) and also, by some authors, for $^{99m}Tc$ MAG3 (*4*). It is obvious that the modification of extraction efficiency invalidates the stationarity condition.
- For the deconvolution of a renogram, a precordial curve is usually used as the input function. It is well demonstrated that a precordial curve often differs from a plasma curve because of the interstitial activity included in the precordial region of interest (ROI) (*5,6*). Because tracer kinetics in the tissue differ from those in the plasma,