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Localization of parathyroid enlargement: experience with technetium-99m methoxyisobutylisonitrile and thallium-201 scintigraphy, ultrasonography and computed tomography

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Abstract. Technetium-99m methoxyisobutylisonitrile (MIBI), like thallium-201, has recently been introduced as a myocardial perfusion agent and is now also showing very promising results in parathyroid scintigrapy. The results of ^{201}Tl/^{99m}Tc-pertechnetate and ^{99m}Tc-MIBI/^{99m}Tc-pertechnetate subtraction scintigraphy, ultrasonography and computed tomography are presented in a series of 43 patients operated on for hyperparathyroidism. All four imaging modalities were confirmed to be reliable, scintigraphy being the most accurate. Sensitivities ranged from 81% to 95%, that of ^{99m}Tc-MIBI being the highest. Moreover this tracer, which has more favourable physical and also biochemical properties, yielded images of superior quality. This allowed localization of the lesion by visual inspection only in as many as 86% of the patients with positive ^{99m}Tc-MIBI/^{99m}Tc-pertechnetate subtraction scintigraphy. We believe that the higher sensitivity, superior image quality and lower cost of ^{99m}Tc-MIBI imaging will make ^{99m}Tc-MIBI the new radiopharmaceutical of choice for parathyroid scintigraphy (when one takes into account the stability of labelling with large activities it is possible to perform three or four cardiac studies together with one parathyroid scintigraphic examination using one lyophililzed vial).

Key words: Thallium-201 — Technetium-99m methoxyisobutylisonitrile — Computed tomography — Ultrasonography — Parathyroid

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Introduction

Thallium-201/technetium-99m pertechnetate ($^{99m}TcO_4$-) subtraction scintigraphy, first introduced in the early 1980s [1], is one of the most reliable imaging modalities for localization of parathyroid enlargement. Nevertheless, ^{201}Tl cannot be considered an ideal tracer, owing to both its physical properties (low photon energy and a relatively long half-life) and its biochemical characteristics (it is not a parathyroid-specific tracer, but serves as an index of perfusion and cellular density) [2]. These drawbacks are accentuated by the closely adjacent thyroid tissue: since the thyroid is also a highly vascular and cellular gland, it takes up ^{201}Tl avidly. For this reason subtraction techniques are utilized which exploit the different biological behaviour and tissue distribution of two tracers, namely the thyroid-specific $^{99m}TcO_4$- uptake relative to the more diffuse perfusion-dependent distribution of ^{201}Tl. A variety of different acquisition and subtraction protocols have been used [2–12] and this, together with the different patient populations studied, probably explains the wide range of sensitivities reported (26%–94%) [13–15] (a positive correlation seems to exist between lesion size and its correct scintigraphic localization) [10]. It is believed that the technique may be highly operator dependent and that there is a need for methodological modifications, particularly to standardize acquisition and processing protocols [16–18]. When optimized, the procedure generally has high sensitivity (75%–91%) [19]. In an attempt to improve the technique further, modifications of the acquisition or processing protocols continue to be proposed [16, 17]. The current role of scintigraphy in the localization of parathyroid enlargement remains the subject of considerable debate [20–23]. For these reasons there is significant interest in the development of better tracers for parathyroid scintigraphy. Methoxyisobutylisonitrile (MIBI), like ^{201}Tl, distributes primarily in proportion to tissue blood flow [24, 25] and was first introduced for the assessment of myocardial perfusion [24, 26, 27]. Being a technetium chelate, the new tracer will overcome the physical drawbacks of ^{201}Tl and in 1989 it was proposed for parathyroid scintigraphy [28].

^{99m}Tc-MIBI/iodine-123 subtraction scintigraphy was demonstrated to be at least as accurate as $^{201}Tl/^{99m}TcO_4$- subtraction scintigraphy in localizing enlarged parathyroid glands [29] and was also shown to display high sensitivity when imaging was performed at two time points. The early images after ^{99m}Tc-MIBI injection were taken as the thyroid phase and the late acquisition (2–3 h later) as the parathyroid phase [30].

The aim of this paper is to compare our results using ^{99m}Tc-MIBI/$^{99m}TcO_4$- and $^{201}Tl/^{99m}TcO_4$- subtraction scintigraphy, ultrasonography and computed tomography (CT) in 43 patients operated on for hyperparathyroidism.

Materials and methods

One hundred and eight patients referred for suspected hyperparathyroidism were entered into the study and underwent $^{201}Tl/^{99m}TcO_4$- and ^{99m}Tc-MIBI/$^{99m}TcO_4$- subtraction scintigraphy, ultrasonography and CT. In addition ten control subjects (two normal volunteers, five non-hyperparathyroid hypercalcaemic patients, two patients with multinodular goitres and one patient with a thyroid cyst) were studied similarly, except that CT was not performed. The 43 patients who have to date undergone surgical exploration and confirmation are the principal subject of this report.

Scintigraphy was performed by means of a small field of view gamma camera (S.E.L.O., Italy), equipped with a parallel-hole, high-resolution collimator and a zoom factor of 1.5, on line with a microcomputer (Link System, UK). Data were recorded in 128 × 128 word matrix. The following acquisition protocols were utilized:

$^{201}Tl/^{99m}TcO_4$-scintigraphy. 40 MBq of $^{99m}TcO_4$- was administered by i.v. injection and was followed after 15 min by dynamic acquisition of ten 60-s frames, using simultaneous dual-energy windows (20%) centered on the 80- and 140-keV photopeaks. Subsequently 80 MBq of ^{201}Tl was injected i.v., and 5 min later a similar dual-energy dynamic acquisition of 15 60-s frames was performed.

^{99m}Tc-MIBI/$^{99m}TcO_4$- scintigraphy. 40 MBq of $^{99m}TcO_4$- was administered by i.v. injection and was followed after 15 min by dynamic acquisition of ten 60-s frames using a 20% window centered at the 140-keV photopeak. Subsequently 400–500 MBq of ^{99m}Tc-MIBI was injected i.v. and commencing 120 s later, a series of 20 60-s frames was acquired.

Scans were read after normalizing the ^{201}Tl and ^{99m}Tc-MIBI images to the $^{99m}TcO_4$- images and subtraction was accomplished by choosing a correction factor which best adjusted the average counts in the thyroid area to the same level as that in surrounding tissues. This avoids false-negative results in cases of parathyroid adenomas lying within the thyroid region of interest.

In $^{201}Tl/^{99m}TcO_4$- subtraction scintigraphy the first image recorded in the 80-keV peak, at the time when only $^{99m}TcO_4$- had been administered, was used for scatter correction of ^{99m}Tc gamma rays into the ^{201}Tl k-x-ray emission window.

Ultrasonography was performed scanning in the longitudinal and transverse planes, using a Hitachi 7.5-MHz linear probe.

CT was performed using G.E. 9008 High Light equipment, acquiring 3-mm-thick slices in a 512 × 512 matrix before and after i.v. injection of 150–200 ml (flow rate of 2 ml/s) of a nonionic contrast medium, Iopamidolo (Bracco, Italy), with an iodide concentration of 370 mg/ml.

Results

In normal volunteers and in patients with hypercalcaemia due to causes other than hyperparathyroidism, without palpable thyroid nodules, no mismatched areas of ^{201}Tl or ^{99m}Tc-MIBI versus $^{99m}TcO_4$- concentration were observed.

In the presence of solid thyroid nodules, significant uptake of ^{201}Tl and ^{99m}Tc-MIBI (generally higher than in the surrounding tissue) was observed whether or not the lesions showed uptake of $^{99m}TcO_4$-. As expected, thyroid cysts did not concentrate any tracer and neither did one almost exclusively cystic parathyroid lesion (see below).

Of the 43 patients thus far operated on for hyperparathyroidism, one was excluded from further analysis in this series because, despite secondary hyperparathyroidism diagnosed on clinical and biochemical grounds, no localization was obtained by any of the four imaging modalities utilized, and furthermore surgical exploration did not reveal any site of parathyroid enlargement.

Of the remaining 42 patients, one had a large, almost exclusively cystic parathyroid adenoma, which, although located by both ultrasonography and CT, was interpreted as being a thyroid lesion (multinodular goitres being endemic in our area) and thus failed for parathyroid lesion location.

$^{201}Tl/^{99m}TcO_4$- demonstrated the lesion(s) in 36 patients (sensitivity 86%) while ^{99m}Tc-MIBI located the lesion(s) in 40 cases (sensitivity 95%). In 38 of them a single adenoma was present; one patient had two adenomas, and one had three. As the large majority of lesions were solitary, sensitivity was calculated for patients, interpreting a location to be correct only when all enlarged glands were correctly diagnosed. Although hyperplastic glands were localized in a few patients suffering from secondary hyperparathyroidism, they were not entered into this series as they have thus far not undergone surgery.

Only two patients had a previous history of surgery for hyperparathyroidism; few conclusions can be drawn from such a small number. It is worth noting that in the detection of mediastinal adenomas, the sensitivity of ultrasonography dropped dramatically, as expected (0/4), but surprisingly the sensitivity of CT was also low (1/4).

In all but one of the cases, ^{99m}Tc-MIBI showed a qualitatively higher lesion-to-background ratio than

Table 1. ^{201}Tl and ^{99m}Tc-MIBI uptake in thyroid and parathyroid, normalized for 100 pixels and corrected for the previously injected $^{99m}TcO_4$- contribution in the different areas in six patients with parathyroid adenomas which, being outside the thyroid area, could be used to calculate uptake ratios

Patient	^{201}Tl			^{99m}Tc-MIBI		
	T	P	P/T	T	P	P/T
V.M.	4539	4802	1.058	13797	17959	1.302
B.M.	3141	3448	1.098	18157	21625	1.191
M.V.	3655	2941	0.805	36900	49333	1.337
V.F.	2864	2860	0.999	10732	22262	2.074
F.D.	8918	7103	0.796	41541	63009	1.515
G.P.	2390	1797	0.752	25958	31437	1.211
			0.918±0.151* (mean ±SD)			1.439±0.332* (mean ±SD)

T, Thyroid counts; P, parathyroid counts; P/T, parathyroid over thyroid uptake
* P=0.015 (two-tailed Student's t-test)

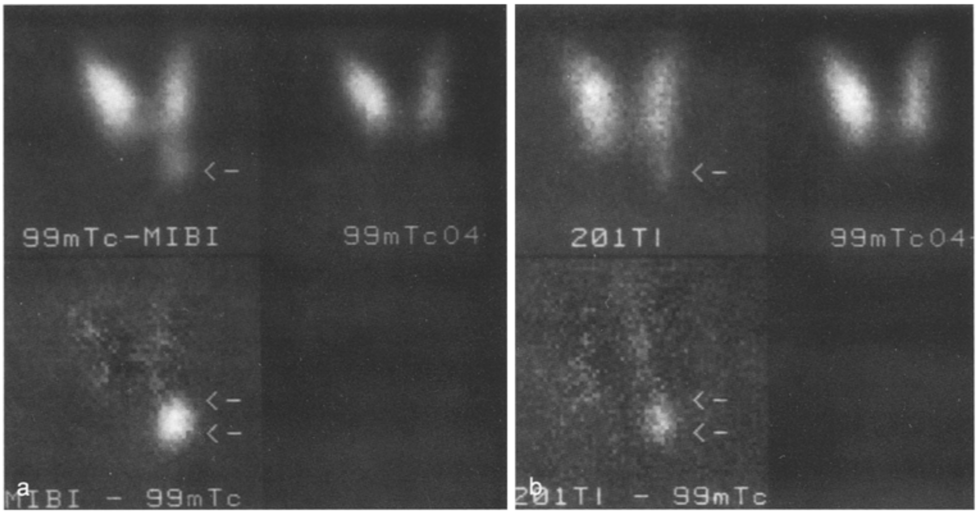

Fig. 1. a Patient F.M. *Top left:* ^{99m}Tc-MIBI; *top right:* $^{99m}TcO_4$-; *bottom left:* ^{99m}Tc-MIBI– $^{99m}TcO_4$-. **b** Same patient as in **a**. *Top left:* ^{201}Tl; *top right:* $^{99m}TcO_4$-; *bottom left:* ^{201}Tl- $^{99m}TcO_4$-. The patient had a left inferior parathyroid adenoma (*arrows*)

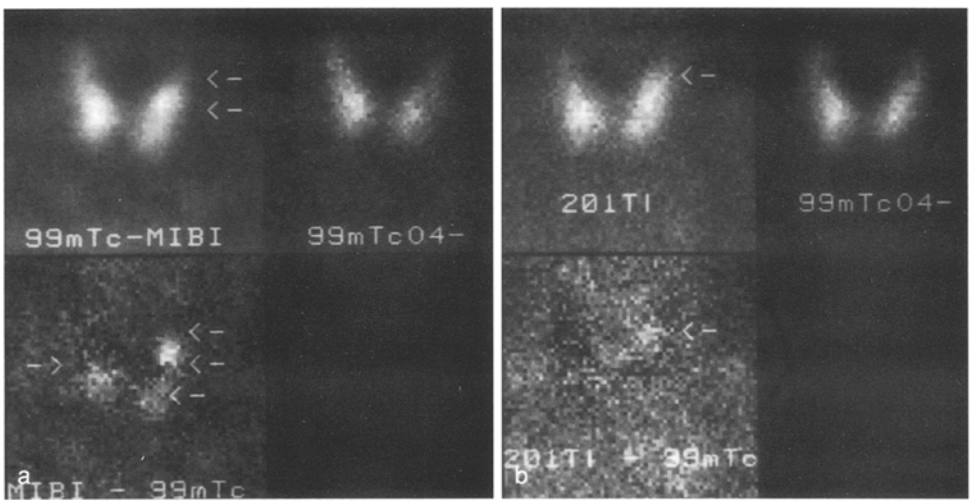

Fig. 2. ***a*** Patient E.S. *Top left:* ^{99m}Tc-MIBI; *top right:* $^{99m}TcO_4$-; *bottom left:* ^{99m}Tc-MIBI- $^{99m}TcO_4$-. ***b*** Same patient as in ***a***. *Top left:* ^{201}Tl; *top right:* $^{99m}TcO_4$-; *bottom left:* ^{201}Tl– $^{99m}TcO_4$-. Three parathyroid adenomas — superior, inferior left and inferior right (*arrows*) — were present in this patient with tertiary hyperparathyroidism

^{201}Tl. This observation was objectively confirmed by regions of interest defined over the parathyroid adenoma and adjacent thyroid tissue in six patients (after correcting the ^{201}Tl and ^{99m}Tc-MIBI uptake in the thyroid and parathyroid areas for the previously injected $^{99m}TcO_4$- and normalizing counts for 100 pixels) in whom the adenomas were separate from the thyroid tissue but did not lie in the mediastinum. In these cases a higher count rate should be expected for the ^{99m}Tc chelate due to the higher energy photons (Table 1). Statistical comparison (two-tailed Student's t-test) showed these differences to be significant (P=0.015).

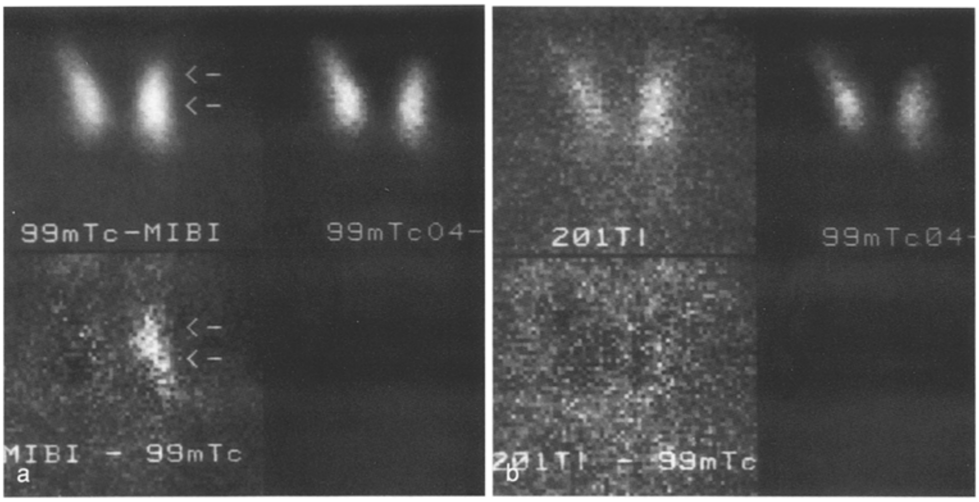

Fig. 3. ***a*** Patient DD. *Top left:* ^{99m}Tc-MIBI, *top right:* $^{99m}TcO_4$-; *bottom left:* ^{99m}Tc-MIBI– $^{99m}TcO_4$-. ***b*** Same patient as in a. *Top left:* ^{201}Tl; *top right:* $^{99m}TcO_4$-; *bottom left:* ^{201}Tl- $^{99m}TcO_4$-. This patient had a left superior parathyroid adenoma (*arrows*) (size, 2×1 cm)

The ^{99m}Tc-MIBI yielded images of clearly superior quality (Fig. 1) which allowed detection of the adenoma by visual inspection of the tracer distribution alone in 34 of the 40 patients (85%) in whom ^{99m}Tc-MIBI/$^{99m}TcO_4$- subtraction scintigraphy correctly located lesions. In this group of patients the computer-assisted subtraction protocol merely confirmed the diagnosis, while in the remaining six patients (15%) the lesion could not be localized without this technique. In one patient with tertiary hyperparathyroidism and three enlarged parathyroids (0.8, 1.4 and 1.8 cm), ^{99m}Tc-MIBI/$^{99m}TcO_4$- subtraction scintigraphy was able to locate all these tumours (Fig. 2a), while visual comparison of ^{99m}Tc-MIBI/$^{99m}TcO_4$- images and ^{201}Tl scintigraphy demonstrated only the largest lesion at the upper pole of the left thyroid lobe (Fig. 2b).

Ultrasonography and CT correctly detected the lesions in 34 and 35 patients (sensitivity 81% and 83%) respectively. One patient with secondary hyperparathyroidism suspected on clinical and biochemical grounds was operated on although all four imaging modalities yielded negative results; no lesion could be found despite extensive surgical exploration.

Discussion and conclusion

The initial observation that the uptake of ^{99m}Tc-MIBI was enhanced in solid thyroid nodules could have been anticipated given the higher blood flow and cellularity which are frequently found in these lesions; confirmation in larger series is, however, needed. Thyroid-stimulating hormone control is known not to be a major factor in ^{99m}Tc-MIBI uptake by thyroid tissue [27, 31]. Only one of our patients with thyroid nodules underwent surgery and in this patient a Hürthle cell carcinoma was found. This lesion corresponded to a focus of increased ^{99m}Tc-MIBI concentration as compared to normal surrounding tissue and ^{201}Tl uptake was even greater. Unfortunately the imaging protocol did not include early and delayed scans, so no comment can be made as to any possible difference in washout of ^{99m}Tc-MIBI from thyroid and parathyroid nodules [30]. While it has been reported that parathyroid lesions retain ^{99m}Tc-MIBI longer than thyroid tissue, it is worth noting that persistent uptake of the tracer 4 h after injection has been reported in a medullary thyroid carcinoma (although a more favourable tumour-to-background ratio was present in the early acquisition) [32]. A similar observation has been made by Taillefer et al. in a case of follicular adenoma [30].

^{201}Tl and ^{99m}Tc-MIBI parathyroid scintigraphy, ultrasonography and CT were all demonstrated to be reliable in locating parathyroid enlargement, with sensitivities ranging from 81% to 95%, scintigraphy being the most accurate modality. ^{201}Tl and ^{99m}Tc-MIBI scintigraphy gave relatively similar results and showed an excellent correlation, although the sensitivity of the new tracer was higher. Figure 3a is an example of a left superior parathyroid adenoma (size, 2×1 cm) correctly located by ^{99m}Tc-MIBI in spite of a negative ^{201}Tl study (Fig. 3b). In addition we wish to emphasize that more favourable uptake ratios for ^{99m}Tc-MIBI in parathyroid adenomas versus surrounding tissues were observed in all but one lesion (not included in Table 1 as it was located inside the thyroid region of interest). This lesion was made up exclusively of oxyphilic cells, which is an unusual histological pattern for parathyroid lesions. Unfortunately this does not improve our understanding of the exact mechanism of ^{99m}Tc-MIBI uptake in parathyroid adenomas, which seems to be a consequence of multifactorial influences including the biochemical properties of the tracer (lipophilicity and cationic charge) and local factors such as blood flow, transcapillary exchange, interstitial transport and negative intracellular charge of both mitochondria and membranes [25].

The high target-to-background ratio, together with the superior image quality due to the physical properties of ^{99m}Tc as a radiolabel, permitted the detection of adenomas without any subtraction processing in a very large majority of the patients. This result might have been expected as a consequence of the favourable uptake ratio, the lesser degree of scatter and absorption of the 140-keV photons of ^{99m}Tc and the higher count rates which are the consequence of the injection of larger activities of the ^{99m}Tc chelate. The latter could be achieved safely because the radiation dose to the patient has been demonstrated to be approximately 10–20 times less for ^{99m}Tc-MIBI than for ^{201}Tl when the same activity is injected [28] (whole-body radiation doses for ^{201}Tl=0.0555 mGy/MBq vs 0.0041 mGy/MBq for ^{99m}Tc-MIBI). These factors not only result in an improvement in sensitivity, but also make the scan easier to read and less operator dependent, which may contribute to more uniform and satisfactory diagnostic results.

The subtraction of thyroid from parathyroid imaging which, when using $^{99m}TcO_4$- and ^{201}Tl, may be readily performed as a consequence of photon emissions of different energies, was achieved by first injecting a small amount of $^{99m}TcO_4$-, the distribution of which does not significantly interfere with the subsequent image of ^{99m}Tc-MIBI distribution which is obtained after injecting a much larger amount of the second ^{99m}Tc-labelled tracer (ratio 10 or 12: 1). An alternative solution is that of Coakley and co-workers, who used ^{123}I as the tracer for thyroid mapping [28, 29]. ^{123}I is certainly ideal for thyroid imaging due to its metabolic properties and the energy of its gamma emission; however, it is expensive and not always available. Finally, Taillefer et al. proposed a dual-phase scintigraphic technique after injecting ^{99m}Tc-MIBI alone [30]. The initial image was considered as the thyroid phase while the image obtained after 2–3 h was considered as the parathyroid phase due to the differential washout of normal thyroid tissue and enlarged parathyroid glands. This approach is interesting as it could avoid many of the drawbacks of subtraction protocols. Nevertheless, a normal thyroid gland seems to be necessary because thyroid lesions may show altered ^{99m}Tc-MIBI clearance. In fact Taillefer et al. had a false-positive study in a patient with a follicular adenoma. A deeper knowledge of the mechanism of ^{99m}Tc-MIBI uptake and metabolism in various types of thyroid lesions is needed and Taillefer et al. suggest that the thyroid subtraction map should be obtained by means of another tracer in selected cases. We thus believe that such a technique may be suboptimal in geographic areas where a significant incidence of thyroid nodules occurs (as is the case in our region).

As a radiopharmaceutical ^{99m}Tc-MIBI has the further advantage of always being available as a lyophilized MIBI kit which can be labelled in a single step. ^{201}Tl was first proposed for myocardial perfusion studies, and ^{99m}Tc-MIBI is also primarily used for this purpose. While the cost of ^{99m}Tc for labelling is negligible, the lyophilized kit is expensive; however, because the chelate is very stable even when labelled with high activities of ^{99m}Tc, it is possible to obtain from one lyophilzed vial sufficient tracer for either three or four cardiac studies and one parathyroid scintigraphic study. In these circumstances the cost falls below that of ^{201}Tl.

Scintigraphy, ultrasonography and CT will continue to play a major role in localizing enlarged parathyroid glands. We were unable to compare the performance of magnetic resonance imaging (MRI) as it was not available in our institution at the time. The role of this technique, which has been used to a limited extent over the last 10 years to localize enlarged parathyroids [31–36], has still not been fully defined. MRI is certainly attractive given its ability to permit imaging in the sagittal, coronal and transaxial planes, the lack of exposure to ionizing radiation, the excellent delineation of vascular structures without the need for contrast, the excellent spatial resolution and the fact that it enables some degree of in vivo tissue characterization. Nevertheless, MRI has not been shown to improve the localization of enlarged parathyroid glands significantly above that achieved by other techniques [33–36]. This, together with its high cost and somewhat limited availability, prevent MRI from being a routine screening test.

We thus believe that ^{99m}Tc-MIBI is the new tracer of choice for parathyroid scintigraphy and foresee that it may gradually replace ^{201}Tl for this indication in the majority of nuclear medicine units.

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