and healthy, high-calcitonin, 3.8% (0.8%) (p < 0.001 vs either the normal group or the cancer group).

Dose–dilution curves for plasma from both normal subjects (9) and patients with medullary thyroid carcinoma (14) paralleled the standard curve. In contrast, dose–dilution curves for unextracted plasma from the healthy, high-calcitonin group uniformly deviated from the standard curve; examples are shown in Figure 2. Dose–dilution curves for extracts of plasma from this group were indistinguishable from those of authentic hormone (Figure 2).

Response to calcium infusion. All five members of the healthy, high-calcitonin group had normal responses to induced hypercalcemia when assessed by the extraction technique (Figure 3).

Discussion

Radioimmunoassay of calcitonin is widely used to detect and aid in post-surgical management of the calcitonin-secreting neoplasm, medullary thyroid carcinoma (1–3). In this context—i.e., family screening and postoperative testing—such testing has been highly-effective, with a very low false-negative rate (2) and an acceptably low false-positive rate (1, 2, 15, 16). Nonetheless, there are problems with calcitonin assay that we have discussed extensively elsewhere (13, 17). Some groups, on the strength of above-normal values for immunoreactive calcitonin in plasma, have done thyroid gland explorations and removals that revealed no thyroid abnormalities (15, 16). We found no thyroid gland disease besides Hashimoto's thyroiditis in two female members of a family having multiple endocrine neoplasia, type 2; their values for whole-plasma calcitonin were high pre-operatively but were unchanged after total thyroidectomy (unpublished results).

Although there are hints in the literature (15, 16), there are no systematic studies of these relatively rare persons who seem to be healthy but have clearly above-normal values for immunoreactive calcitonin in plasma. Ordinarily, healthy individuals would not have the test done, but because we have made calcitonin measurements in a large number of normal volunteers, we have found four such persons over a 10-year period, and one other, accidentally found, has been referred to us. Our immunochemical studies suggest that none of these men had above-normal concentrations of authentic calcitonin in their plasma. First, their plasmas yielded dose–dilution curves that were not parallel to those of standard calcitonin. Second, the fraction of their whole-plasma calcitonin-like immunoreactivity that was silica-extractable was very low compared with plasma from normal persons and those having medullary thyroid carcinoma. Third, the absolute values for extractable calcitonin in plasma were normal in the healthy, high-calcitonin group, but remained high in samples from the cancer patients. Finally, the responses of the extractable calcitonin to intravenous calcium were normal in the healthy, high-calcitonin group.

These "healthy, high-calcitonin" men have each undergone detailed, specific evaluations by their personal physicians without any findings to indicate sporadic or familial medullary thyroid carcinoma, multiple endocrine neoplasia, other neoplasms, or any of the other various conditions reportedly associated with increased plasma calcitonin (18). Under careful scrutiny, none has developed relevant medical problems during follow-up now extending to seven years.

Fig. 2. Dose–dilution curves for immunoreactive calcitonin of unextracted plasma (closed symbols, thin solid line) and silica extracts of plasma (open symbols, dashed line) compared with authentic calcitonin standard (heavy solid line)

Samples came from two seemingly healthy men with increased calcitonin-like immunoreactivity in unextracted plasma. Note nonparallelism of unextracted plasma curves with each other and with the standard; plasma extracts gave fully parallel dilution curves

Fig. 3. Response of concentrations of silica-extractable calcitonin to infusion of Ca (2 mg of elemental Ca per kg body wt. over 5 min) in seemingly healthy men with above-normal calcitonin-like immunoreactivity in unextracted plasma

The boxed area ("normal range") indicates the absolute limits of responses for 30 normal male controls. The patients' responses were clearly normal
Thus, on clinical grounds as well as the immunochemical data, there is reason to believe that the high calcitonin values are of no significance to their health. Of course, only continued observation of the patients will assure us that they do not have some underlying illness that first manifested itself in the calcitonin measurements.

We conclude that a small part of the healthy population has a circulating factor or group of factors that can interfere in radioimmunoassay of plasma for calcitonin. This factor is not monomeric calcitonin, although our data give no further insight into its nature. The artificiately high plasma calcitonin values thus produced could cause erroneous diagnoses of malignancy and lead to unnecessary surgery (15, 16). The simple technique we have devised for silica extraction of calcitonin from plasma allows distinction of "healthy, high-calcitonin" plasmas from those of patients with medullary thyroid carcinoma. This may be accomplished on a single plasma sample, but including the response to a calcitonin secretagogue probably adds further diagnostic certainty. We do not yet know if this technique also differentiates seeming ectopic calcitonin secretion by nonthyroid tumors (7). The relationship of the circulating calcitonin-like factor to heterogeneous forms of immunoreactive calcitonin found in other studies (14, 19) is unknown and deserves further study.

This work was supported in part by grants from the NIH, USPHS (AM-19607, AM-32526, RR-555), and the Mayo Foundation. Dr. Body was successively supported by the Rose and Jean Hoguet Foundation (Brussels) and the Rapoport Fund. We gratefully acknowledge the assistance of J. Blomgren, Deanna Nash, and S. LeBlanc, of the Clinical Study Unit, and J. Rolfe, K. Laasko, M. Fryer, and M. E. Campion, of our laboratory and office staff. Dr. G. W. Sizemore provided samples from patients with medullary thyroid carcinoma.

References