

Improved Diagnosis and Management of Hyper- and Hypothyroidism by Timing the Arterial Sounds

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ABSTRACT. "Sphygmo-Recording," a non-invasive method for timing the arterial pulse wave contour provides an objective measure of responses to medication in patients with hyper- and hypothyroidism. The QK_d interval, *i.e.*, the interval from the onset of the QRS complex (Q) to the onset of the Korotkoff sounds (K) at the brachial artery when the sphygmomanometer cuff is at diastolic pressure (d) is the QK_d interval. QK_d is normally 205 ± 12 msec. In hyperthyroidism the QK_d interval may be

shortened to 110 msec. In hypothyroidism the QK_d interval may be prolonged to 320 msec. Changes in QK_d parallel changes in clinical status and serum total T_4 and T_3 , measured by radioimmunoassay. QK_d can be used as an objective guide to antithyroid therapy in hyperthyroidism and replacement therapy with thyroid hormone in hypothyroid individuals. (*J Clin Endocrinol Metab* 42: 330, 1976)

DESPITE the availability of a large number of chemical tests for the management of patients with thyroid diseases, therapeutic decisions must often be postponed because of delays in laboratory reporting. The generally available physiologic measurements of thyroid function such as the basal metabolic rate and Achilles reflex time are severely limited by measurement error and significant overlap between dysthyroid and euthyroid subjects (1,2).

Studies of myocardial contractility *in vitro* and *in vivo* have demonstrated a remarkable sensitivity of the myocardium to changes in thyroid hormone concentrations (3-5). The physiologic effect of thyroid hormones may therefore be evaluated by assessing changes in myocardial contractility and stroke output by use of the non-invasive technique of Sphygmo-Recording (6-8). Sphygmo-Recording measures the time interval between the onset of the QRS complex of the electrocardiogram (Q), and the arrival of the pulse at the brachial artery, as detected by the generation of arterial Korotkoff sounds (K)

at the antecubital fossa during measurement of arterial blood pressure. The QK interval at diastolic blood pressure (QK_d) has been shown to be remarkably accurate in the diagnostic assessment of thyroid status (8). The QK_d interval can be recorded on any 2-channel phonocardiograph (9), or on a properly modified cathode-ray oscilloscope (10). Most of the recordings in the present study were obtained with a specially designed XY plotter (Hoffman-La Roche Medical Electronics). In normal adults below the age of 70, the QK_d interval has been shown to be limited to a very narrow range, 205 ± 12 msec. (8). In severe hyperthyroidism the QK_d interval may be shortened to as little as 110 msec. In severe hypothyroidism the interval may be prolonged to as much as 320 msec.

We have compared serial Sphygmo-Recording tracings with clinical and chemical findings in 10 patients with hyperthyroidism and three patients with hypothyroidism. The results indicate that the QK_d measurement offers a rapid, non-invasive measure of the end-organ effects of thyroid hormones. This technique is useful in the follow-up of patients during treatment for either hyper- or hypothyroidism.

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Materials and Methods

Hyperthyroid group

Criteria for inclusion included: a) definitive clinical evidence of thyrotoxicosis, b) increased ¹³¹I uptake at 6 and 24 hours, and c) elevated serum thyroxine (T₄) and triiodothyronine (T₃) by radioimmunoassay.

"QK" intervals were obtained with an XY plotter manufactured by Hoffman-LaRoche Medical Electronics Division, or by Sphygmo-Recorder Model SR250 of the City of Hope Medical Center Electronics Instrumentation Division. EKG leads (modified lead I) were applied to the right and left arm of the patient. The indifferent ("ground") electrode was placed on either arm or leg. A sphygmomanometer cuff was applied to either arm. To record Korotkoff sounds, a crystal microphone was placed over the brachial artery. In some studies, an ultrasound transducer was applied under the blood pressure cuff, to detect brachial arterial motion at the time of arrival of each pulse wave. Preliminary studies indicated that results from a conventional microphone (Korotkoff sounds) and results from the ultrasound transducer were virtually identical, with a correlation coefficient of $r = 0.95$. Thereafter, the Korotkoff sound was usually used. The cuff pressure was displayed on the vertical axis. The interval between the onset of the QRS complex and the onset of the

Korotkoff sound (or ultrasound doppler signal) was displayed on the horizontal axis of a print-out card, by means of a DC-stepping motor. Measurements were accurate to ± 2 mmHg and ± 2 msec. As the cuff pressure fell from systolic to diastolic levels, the QK interval shortened, and the calibrated contour of the leading edge of the arterial pressure wave was inscribed (Fig. 1).

Circulating T₄, T₃, and TSH hormones were measured by previously described radioimmunoassay techniques (11-13).

Results

Hyperthyroidism

Table 1 summarizes the clinical features and the initial laboratory data in this group of patients. The clinical courses of 2 patients are described in detail below and in Figs. 2a and b. The data on the remaining 8 patients are given in Figs. 3 and 4.

Case no. 1 (Fig. 2a). A 24-year-old Mexican female was referred because of thyromegaly and exophthalmos. One year before being seen she noted nausea, dysphagia, and proptosis, followed by goiter, heat intolerance, nervousness, proximal muscle weakness, and progressive weight loss (4.5 kg). Physical examination revealed a nervous,

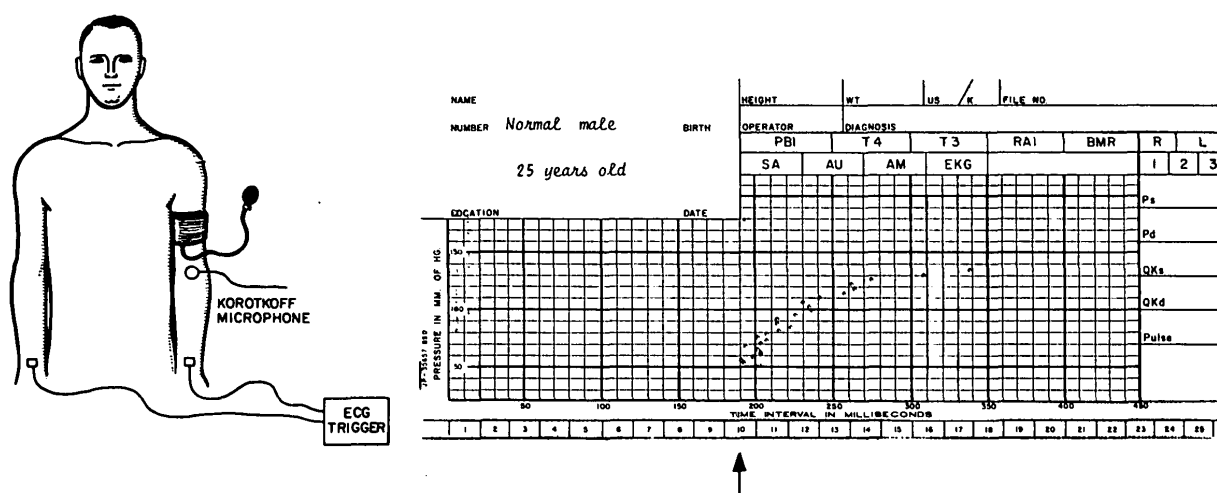


FIG. 1. Automatic plotting of the pulse wave contour at the brachial artery as cuff pressure drops from systolic to diastolic levels. Ordinate = Cuff pressure, Abscissa = QK_d interval. Each dot indicates the onset of the Korotkoff sound. Arrow indicates QK interval at diastolic blood pressure (QK_d) in a normal control subject.

TABLE 1. Initial clinical features and laboratory data

| Fig. | Age | Sex | Initial T ₄ μg/100 ml | Initial T ₃ ng/100 ml | Pretreatment ¹³¹ I uptake 6 h/24 h | Initial QK _d msec | Pretreatment cholesterol mg/100 ml | Initial thyroid size x normal | Exoph- thalmos | Infil- trative der- mopathy | Pre- treatment weight change in Kgs |
|------|-----|-----|-------------------------------------|-------------------------------------|---|------------------------------------|--|--|-------------------|--------------------------------------|---|
| 2a | 24 | F | 66.0 | 1,500 | 55%/55% | 135 | 135 | ×3 | + | - | -4.5 |
| 2b | 52 | F | 25.5 | 800 | 47%/58% | 110 | 154 | ×2 | + | + | -18.2 |
| 3a | 27 | F | 48.0 | 760 | 60%/70% | 120 | 180 | ×2 | - | - | -3.6 |
| 3b | 28 | F | 34.5 | 760 | N.D.* | 150 | N.D. | ×3 | + | + | +3.6 |
| 3c | 34 | F | 29.0 | 605 | 55%/55% | 120 | 135 | ×2 | + | - | -5.5 |
| 3d | 28 | F | 24.0 | 250 | N.D. | 165 | 225 | ×2 | - | - | -31.8 |
| 4a | 33 | F | 20.5 | 370 | 42%/53% | 155 | N.D. | ×2.5 | - | - | -2.3 |
| 4b | 49 | F | 30.0 | 600 | 66%/68% | 120 | 195 | ×2 | - | - | -13.7 |
| 4c | 44 | F | 15.0 | 210 | 65%/75% | 130 | N.D. | ×2.5 | - | - | -2.3 |
| 4d | 67 | M | 15.5 | 330 | 29%/43% | 135 | 182 | Substernal | + | - | -6.8 |

* N.D. = Test not done.

Normal Values:

T₄ = 3-13 μg/100 mlT₃ = 53-190 ng/100 mlQK_d = 205 ± 12 msec

tremulous women with a pulse of 108 and a blood pressure of 140/70 mmHg. Exophthalmos, chemosis, and bilaterally limited external rectus muscle function were present. The thyroid was approximately 3 times the normal size, with bilateral bruits.

A pulmonic systolic ejection murmur, grade 3/6, was present. Ankle edema and infiltrative dermopathy were absent. Laboratory evaluation revealed an initial T₄ of 66 μg/100 ml and a T₃ level of 1500 ng/100 ml. ¹³¹I uptake was 55% at 6 hours and 55% at

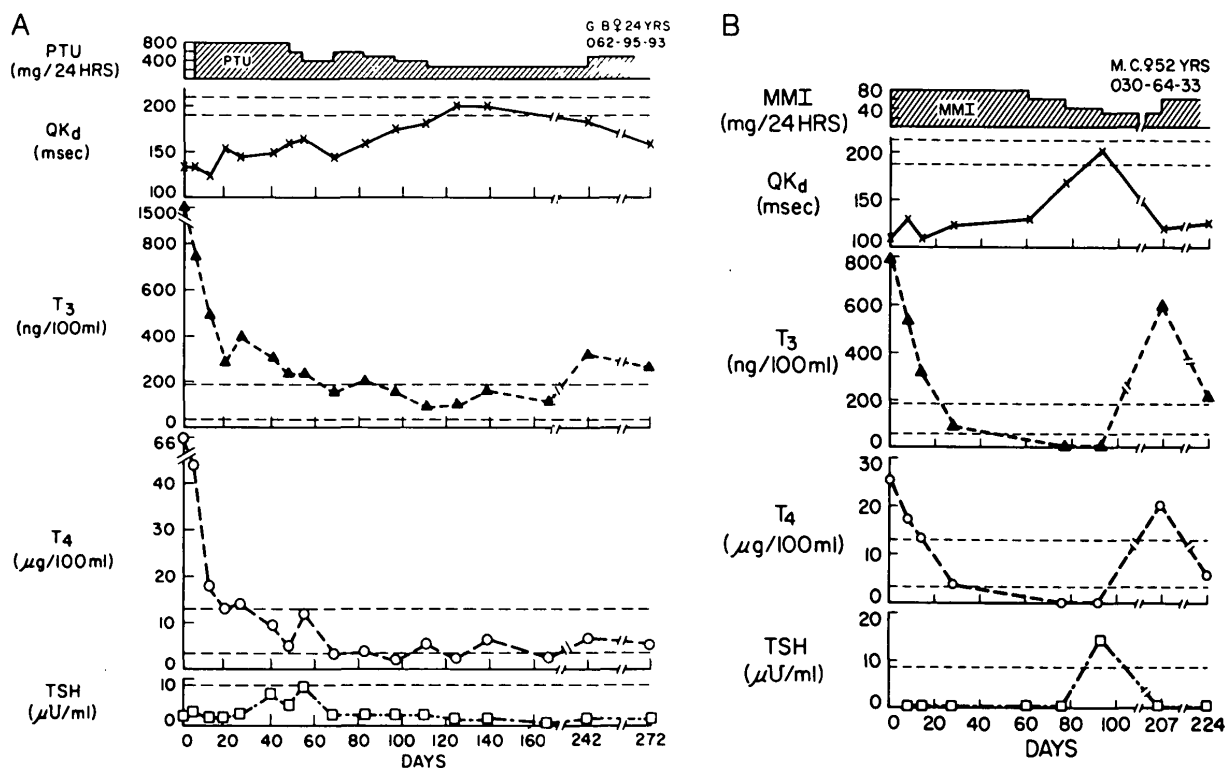


FIG. 2a and b. Patients, G.B. (2a) and M.C., (2b) showing sequential sampling of QK_d, T₃, T₄ and TSH during antithyroid drug therapy (See cases no. 1 and no. 2 in Results section). Dotted lines indicate normal ranges.

24 hours. The thyroid was diffusely enlarged on scan. The QK_d interval on initial examination was shortened to 135 msec.

Propylthiouracil (PTU), 200 mg was given every 6 hours. Gradual clinical improvement was associated with a return of serum T₄ and T₃ levels toward normal. As clinical status improved and circulating thyroid hormone levels became normal, the QK_d interval also gradually returned to normal (Fig. 2a). Coincident with this clinical improvement, PTU dosage was reduced.

Case no. 2 (Fig. 2b). This 52-year-old white female with a history of progressive weakness had an 18 kg weight loss in the year prior to referral. Approximately 9 months prior to evaluation she noted anterior neck swelling, periorbital puffiness, and increased prominence of the eyes. Six months prior to admission, bilateral pretibial swelling and pruritus were noted. Initial physical examination revealed a slender, apprehensive woman with a pulse rate of 117 and a blood pressure of 154/74 mmHg. Exophthalmos, and a diffusely enlarged (approximately 2½ times normal) thyroid gland, with prominent bilateral systolic bruits was palpated. Pretibial infiltrative dermatopathy was present bilaterally. The initial QK_d interval was 110 msec. Initial serum T₄ was 25.5 µg/100 ml, total T₃ was 800 ng/100 ml and TSH was less than 2 µU/ml. An ¹³¹I thyroid uptake was 47% at 6 hours, and 58% at 24 hours. Thyroid scan revealed a diffusely enlarged gland.

Wraps containing Triamcinolone were applied nightly to the involved pretibial areas. Methimazole (MMI) 20 mg was given every 6 hours. QK_d intervals and blood studies were obtained serially (Fig. 2b). After 30 days of treatment with Methimazole, serum T₄ and T₃ levels returned to normal. Gradual lengthening of the QK_d interval to normal paralleled clinical improvement. At 60 days, methimazole was decreased to 30 mg per day. On the 90th day of methimazole treatment a TSH level

slightly above the upper limit of the normal range (14.5 µU/ml) was observed. A rapid normalization of the QK_d interval was associated with depressed serum T₄ and T₃ values at this time. Subsequently the patient took antithyroid medication irregularly for 3½ months. During this period, QK_d shortened to 120 msec as serum T₄ rose to 20 µg/100 ml and serum T₃ increased to 600 ng/100 ml.

Eight other patients had documented laboratory evidence of hyperthyroidism. During therapy, the abnormally shortened QK_d interval became normal as the circulating thyroid hormone values returned to normal (Figs. 3a-d and Figs. 4a-d).

One patient (J.G.), 27 years old, (Fig. 3a) showed an initial brief drop in serum T₃ and T₄ followed by a plateau. The QK_d remained shortened to 140 msec. Because of the patient's non-compliance in taking daily medication, she was pre-treated with

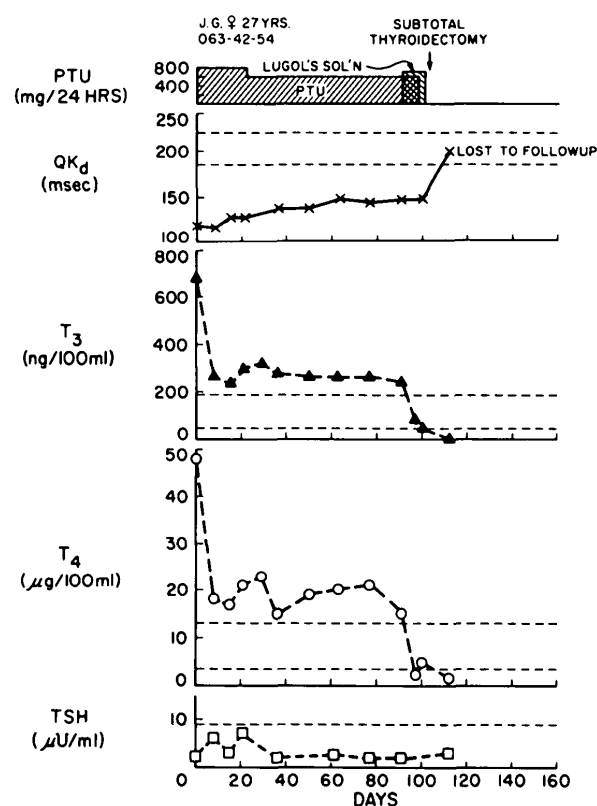


FIG. 3a. Patient J.G. before and after subtotal thyroidectomy.

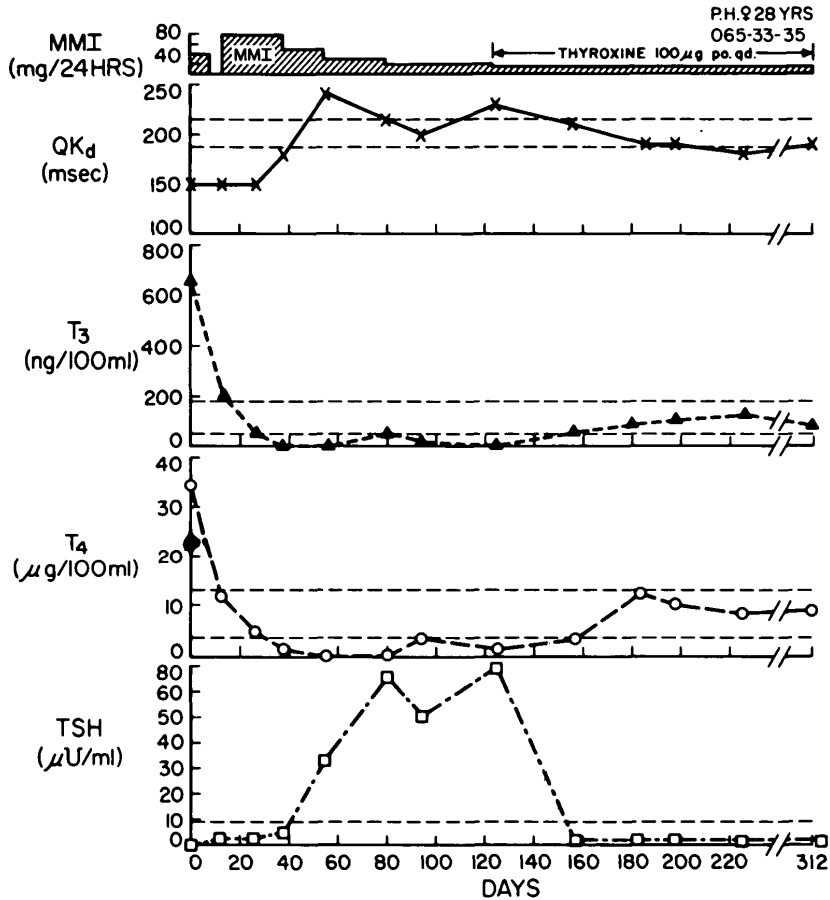


FIG. 3b. Patient P.H. showing overtreatment with methimazole and resultant increase in TSH and prolongation of QK_d interval to 250 msec.

Lugol's solution, following which subtotal thyroidectomy was performed. After surgery, QK_d intervals became normal following a rapid fall of circulating thyroid hormones.

Patient P.H., 28 years old (Fig. 3b), became hypothyroid on modest doses of methimazole. This was associated with abnormal prolongation of the QK_d interval (250 msec) and elevation of TSH levels (70

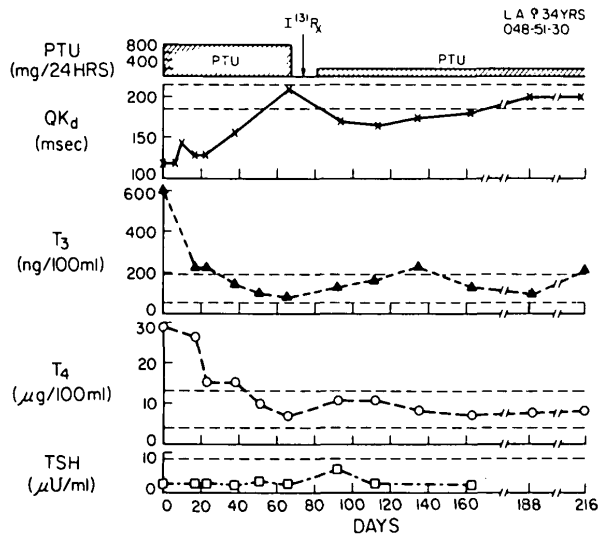


FIG. 3c. Sequential studies of a patient on antithyroid medication.

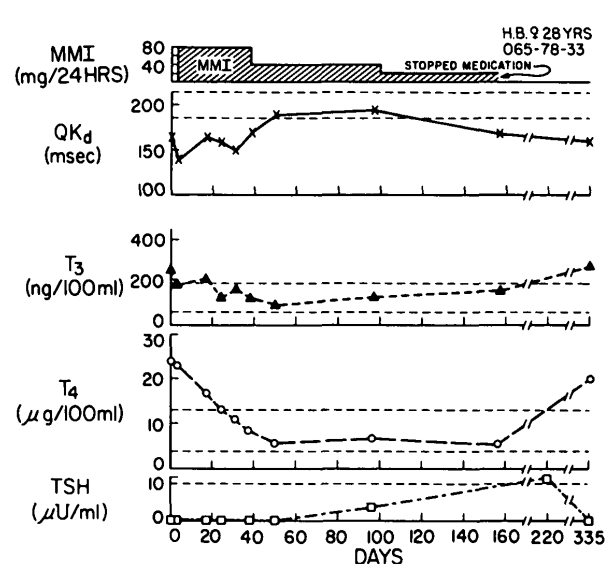


FIG. 3d. See legend for Fig. 3c.

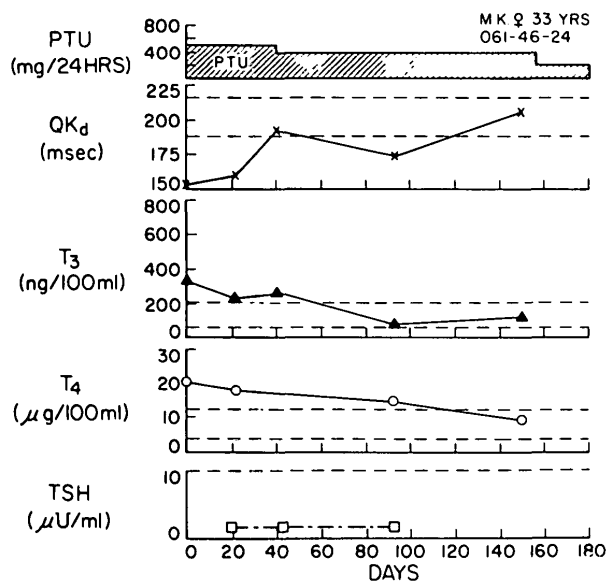


FIG. 4a. Sequential studies of a patient on antithyroid medication.

μU/ml). Subsequently the patient was controlled on methimazole 15 mg daily along with 0.1 mg of L-T₄. Sphygmo-Recordings reflected the decrease in T₄ and T₃ in this patient and paralleled the rising TSH values as an indication of early hypothyroidism.

Except for patient M.C. (Fig. 2b), all patients showed a return of serum T₃ and T₄ values to within the normal range prior to

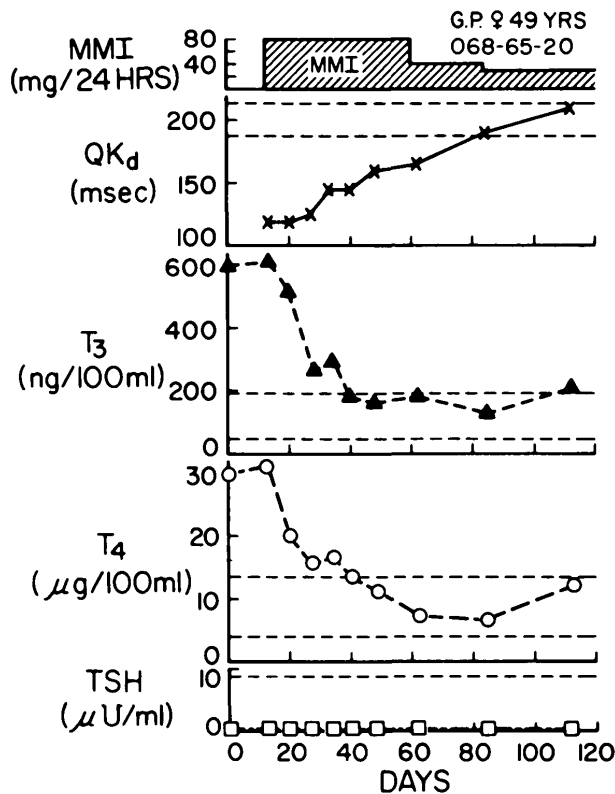


FIG. 4b. See legend for Fig. 4a.

the QK_d interval becoming normal. In no instance was a rise in TSH levels observed without a concomitant prolongation of the QK_d time to normal or into the hypo-

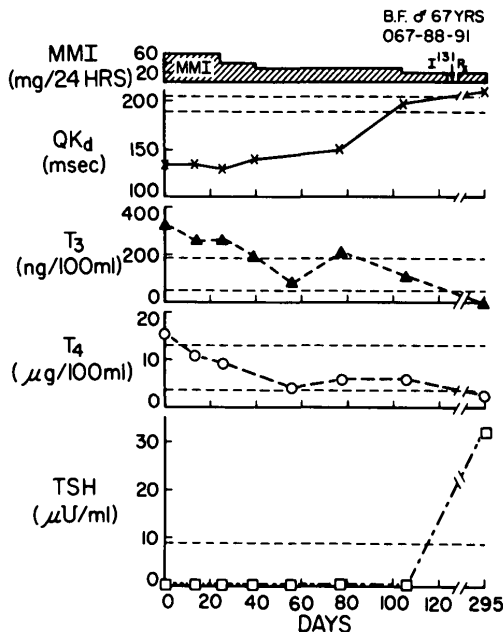
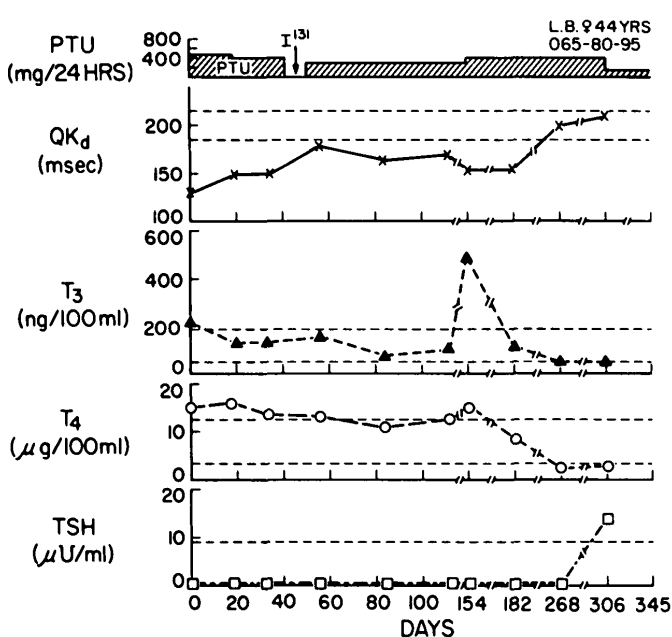


FIG. 4c and d. Patients minimally overtreated with antithyroid medication to illustrate changes in QK_d and TSH.

TABLE 2. Delay between initiation of therapy and return to normal thyroid function tests in 9 patients with thyrotoxicosis*

| Patients | Interval (days) between start of therapy and return to euthyroid range for various tests of thyroid function | | |
|-------------|--|---------------------|-------------------------------|
| | T ₄ days | T ₃ days | QK _d interval days |
| C.B. | 70 | 40 | 115 |
| M.C. | 30 | 15 | 80 |
| J.G. | 100 | 100 | 100 |
| P.H. | 15 | 22 | 42 |
| L.A. | 40 | 50 | 50 |
| M.B. | 25 | 30 | 50 |
| K.M. | 150 | 90 | 150 |
| G.P. | 50 | 50 | 70 |
| F.B. | 60 | 10 | 100 |
| Mean (days) | 60.0 | 45.2 | 85.2 |
| SD | 42.5 | 31.6 | 36.2 |
| SEM | 14.2 | 10.5 | 12.1 |

*Patient L.B. (Fig. 4c) was not included in study since she interrupted her therapy during the observation period.

thyroid range (Figs. 2b, 3b, 4c, and 4d). Frequently, we observed that circulating serum T₃ and T₄ values returned to normal before patients were free of all symptoms suggestive of hyperthyroidism and prior to QK_d intervals becoming normal (Table 2).

Hypothyroidism

Figure 5 shows longitudinal changes in three patients with hypothyroidism. In these, and most patients with hypothyroidism, the QK_d is significantly prolonged beyond the normal range. Some subjects with "borderline" low serum T₄, T₃, and/or "borderline" elevated TSH levels showed "borderline" values for the QK_d measurement.

One of these patients (Fig. 5a) presented secondary amenorrhea but no other clinical stigmata of hypothyroidism. Indeed, thyroid function tests were repeated over a period of several months, because her referring physicians were unable to accept the labora-

tory values in view of the patient's clinical status. Initial QK_d values were also prolonged abnormally into the hypothyroid range (260 msec). With replacement therapy, the QK_d and serum hormone levels promptly returned to the normal range. Spontaneous normal cyclic menses resumed. Subsequently, the patient was placed on birth control pills, and was lost to follow-up. A second case, (Fig. 5b) with no apparent symptomatology of hypothyroidism, was detected in a routine screening procedure for hyperlipidemia. The patient also had a long-standing history of galactorrhea.

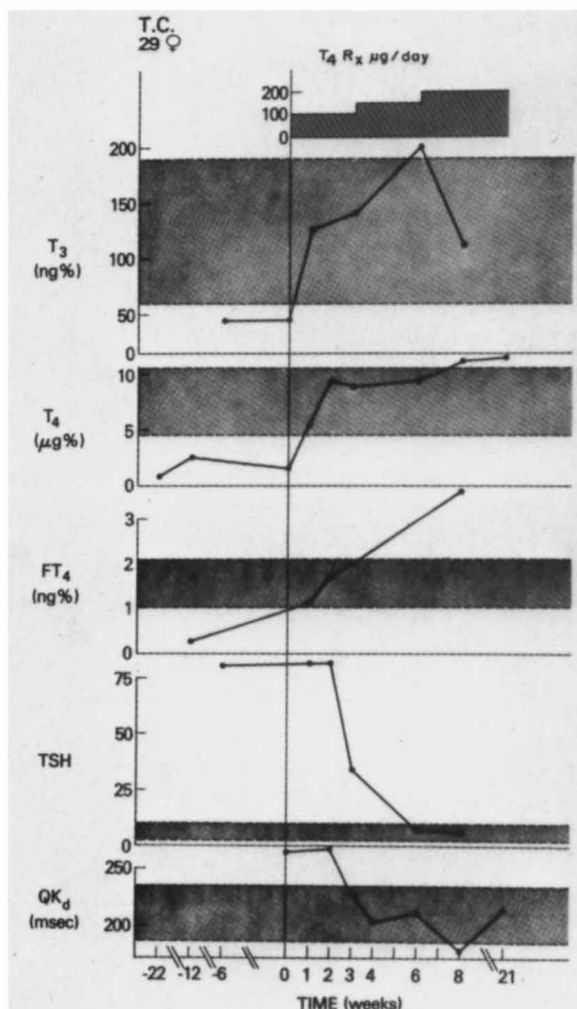
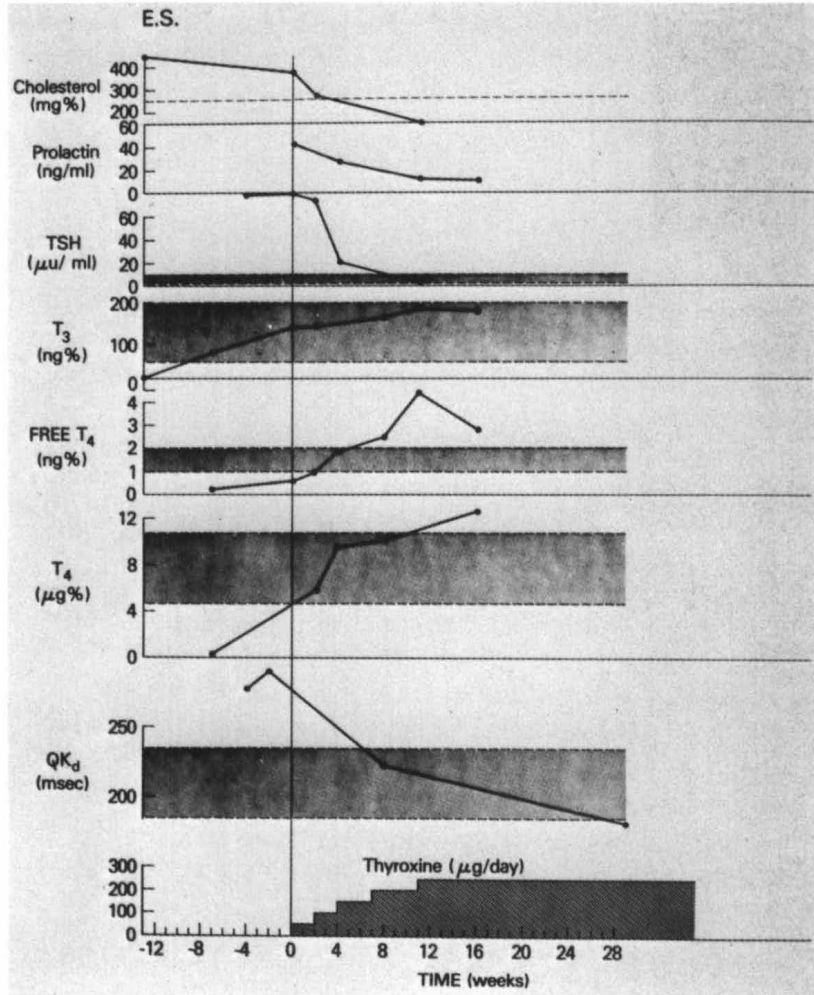


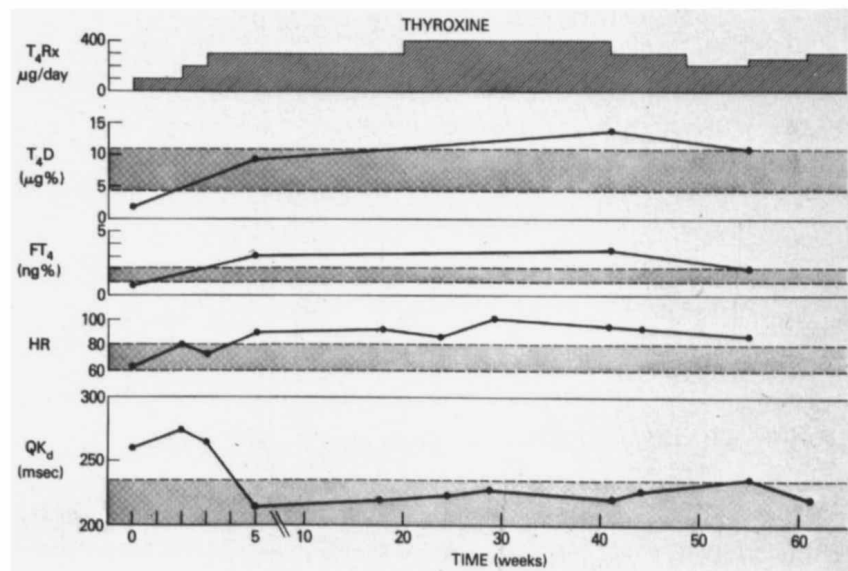
FIG. 5a. Serial changes in QK_d and serum thyroxine, free thyroxine, triiodothyronine, and TSH in three patients with hypothyroidism. 5a) Patient with primary amenorrhea.

FIG. 5b). Patient with hyperlipidemia and galactorrhea with hyperprolactinemia.



K.S. 25 ♀

FIG. 5c). Patient with hypothyroidism secondary to chromoprobe of the pituitary. (H.R. = Heart rate/minute).



Following thyroid hormone replacement, the QK_d and serum thyroid hormone levels returned to normal. Similarly, the initially elevated prolactin levels were suppressed to the normal range and the galactorrhea disappeared.

Case 3 (Fig. 5c) illustrates sequential changes in QK_d and serum thyroid hormone levels in a patient with hypothyroidism secondary to a chromophobe adenoma of the pituitary.

Discussion

Hyperthyroidism

The simple non-invasive technique of Sphygmo-Recording reflected the enhanced myocardial contractility, stroke output, and pulse wave velocity characteristic of thyrotoxicosis. In all patients at the time of initial clinical assessment, QK_d values were at least 4 standard deviations less than the mean of 205 ± 12 msec.

This technique provided us with a means for rapid separation of suspected thyrotoxic patients from the normal population. In addition, follow-up observations utilizing QK_d intervals allowed for immediate adjustments in antithyroid medications.

Because of the ability to evaluate patients during visits, cardiovascular monitoring reduced the possibility of serious overtreatment with antithyroid medication. In no case was an elevated TSH value found that was not associated with a QK_d reading consistent with hypothyroidism or at least at the upper normal range. Like TSH, Sphygmo-Recording appears to be very sensitive to diminished tissue levels of thyroid hormone and parallels all observed elevations in serum TSH.

The follow-up care of patients was facilitated by the availability of the QK_d measurement at clinic visits. QK_d intervals remained consistently shortened as long as serum T_4 and T_3 elevations existed. A shortened QK_d interval was therefore a good indicator for the need of continued high doses of thyroid-blocking agents. Lengthening of the QK_d

interval indicated that the patients were approaching euthyroidism and that a decreased drug dosage was appropriate. Abnormally long QK_d intervals indicated the development of a hypothyroid state and this was met by reduction in antithyroid medication.

The frequent return to normal of circulating T_4 and T_3 values before QK_d intervals returned to within the normal range is impressive. This lag, between serum T_4 and QK_d averaged 25 days in our series of patients (Table 2). A recent report by Toft *et al.* (14) has indicated that in hyperthyroid patients followed serially with serum T_4 , T_3 , and TSH measurements after excessive ^{131}I therapy, there is a similar lag between the subnormal T_4 and T_3 values and the delayed appearance of increased serum TSH. These authors speculated that the metabolic effects of T_3 and T_4 at the hypothalamic and/or thyrotroph level persist for some time after an alteration in circulating thyroid hormone concentration. Likewise, a similar tissue effect may be operative on the myocardium and account for the observed delay in return of QK_d intervals to within the normal range. Other evidence also demonstrates that a finite period of time is required in hypothyroid patients, following treatment with full replacement doses of T_4 intravenously, for clinical symptoms to abate and elevated TSH values to return to normal (15). In addition, recent data indicates that the QK_d returns to normal before the Achilles reflex time (16). Thus Sphygmo-Recording which reflects changes in an end-organ system, the heart, can be used to accurately assess clinical status.

Hypothyroidism

A previous report showed that the technique of Sphygmo-Recording could be useful in the longitudinal follow-up of a patient with hypothyroidism during replacement therapy (6). Our data demonstrate that the prolongation of the QK_d intervals into the hypothyroid range also occurs during treatment with antithyroid medication.

Since the normal replacement dose of thyroid hormone is generally agreed upon, the QK_d measurement is probably of less importance clinically for monitoring therapy in hypothyroidism than in thyrotoxicosis. However, we found it to be a useful guide in making sensitive adjustments in the replacement dose of thyroxine, and it is a useful guide in determining whether the patient is complying with prescribed therapy.

The addition of the QK_d measurement to clinical assessment is particularly useful because at times chemical measurements may be altered independent of clinical thyroid status. Serum total T₃ and T₄ levels are altered in chronic liver disease (17). In pregnancy, and in subjects taking oral contraceptives (18), changes in thyroxine-binding globulin do not affect the QK_d measurement. In rare cases, end-organ insensitivity to circulating thyroid hormones has also been found (19). These limitations have led to searches for methods which rely specifically on end-organ effects. Hypothyroid patients can be separated on occasion by using the Achilles reflex intervals, but only the most severe cases are actually diagnosed by this method (1). Other measures of end-organ function include serum cholesterol, plasma tyrosine, and urinary creatinine concentrations (20). Unfortunately, changes in these compounds are non-specific and are of limited usefulness in thyroid diagnosis. Recently the pre-ejection period (PEP) has been reported to follow changes in circulating thyroid hormone levels (21). The available data on PEP seems to confirm our observations of altered cardiovascular function in thyroid disease. Reza, *et al.* using echocardiography have shown that this non-invasive method may be useful in following patients with depressed circulating thyroid hormone levels (22). Thus attention has focused on cardiovascular responses to thyroid diseases using a number of different techniques.

Sphygmo-Recording may be influenced by alterations in contractility or pulse wave

velocity by changes other than thyroid hormone levels, *e.g.*, in the high output states of acute febrile illnesses or anemia. However, these differences are easily differentiated from the effects of thyroid hormone. Thus, QK_d intervals are shortened in patients with pheochromocytoma, in the immediate post-exercise state, and in the augmented cardiac output induced by heightened adrenergic activity or administration of epinephrine or norepinephrine (9). The interval shortens in subjects above the age of 70, presumably secondary to progressive aortic rigidity and a resulting accelerated pulse wave velocity. Prolonged QK_d intervals have been reported in aortic valvular stenosis, ventricular conduction defects (23), beta-adrenergic blockade (24), and during the administration of Halothane anesthesia (25).

Sphygmo-Recording therefore appears to be a useful screening test for differentiating hyper- or hypodynamic cardiovascular states as well as in estimating the level of thyroid function. The method facilitates the adjustment of antithyroid medication during treatment of hyperthyroidism, or of replacement therapy with thyroid hormone for hypothyroidism.

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