THE COMPUTER IN THE DIAGNOSIS OF THYROID DISEASE

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Introduction of the computer into the medical realm has resulted in many practical applications for its use (*1–3*). This fact is directly related to the computer's ability to store large quantities of information and to process this information on command, its accuracy in fulfilling assigned tasks, and its virtual tirelessness and independent operation. In the realm of the thyroid, computer applications have included analysis of a thyroid model (*4*), diagnosis of certain disease states (*5–8*), assessment of thyroid scans (*9*), and evaluation of the thyroidal radioactive iodine (^{131}I) uptake (*10*).

In a recent study from this laboratory (*11,12*), the merits and reliability of a valuable parameter of thyroid function, the serum-free thyroxine index-T_4 (FTI-T_4), were reported. The availability of a compact and relatively inexpensive programmable electronic computer-calculator system permitted investigation of its use in processing laboratory data for determining the FTI-T_4 and for mathematically estimating thyrometabolic status.

METHODS AND MATERIALS

Serum samples were obtained from 137 normal, 160 "normal," 70 hyperthyroid, and 50 hypothyroid subjects. Normal subjects consisted of 114 male and 23 nonpregnant female blood donors who were clinically healthy and euthyroid, and had taken no medications for at least 2 months before sampling. The group designated "normal" was composed of either euthyroid hospitalized individuals or ambulatory subjects who were pregnant or were taking medications which included estrogens and androgens. No effort was made to select these patients or to determine whether or not they reflected the general population of patients. In addition, euthyroid patients on thyroid replacement therapy for euthyroid goitrous disorders were also included in this category. The hyperthyroid and hypothyroid subjects were unselected except for their underlying thyroid pathology. Many were taking various medications including estrogens. They were classified as to their thyroid diagnosis by history, clinical appearance, and multiple diagnostic laboratory procedures which included radioactive iodine uptake (RAI), scan, and triiodothyronine suppression test, but did not include the laboratory tests under study.

T_4D (*13*), RT_4, and FTI-T_4 values were obtained on each serum sample by manual and visual calculations in the usual manner. For comparison, the same basic data printed out from isotopic counting equipment was applied to a programmed computer-calculator to accomplish the following sequence of calculations for each unknown sample. First, the T_4D was calculated from the standard curve and the value retained in the computer memory. Next, the RT_4 ratio was computed and multiplied by the T_4D to obtain the FTI-T_4 value. Lastly, the value for the FTI-T_4 was categorized as euthyroid, hypothyroid, or hyperthyroid, and the results were printed out on a teletypewriter.

To use the computer to calculate the T_4D, the standard curve was applied first by entering the ordinate values for each abscissa value of 0, 1, 6, 12, 18, and 24 mg% of thyroxine, respectively. Ordinate values were calculated as the percent of isotopic thyroxine bound to thyroxine binding globulin (TBG) compared with the total isotopic thyroxine added to the resin-TBG system (*11*). All data were entered into the computer on punched paper tape through a teletype input/output reader integrated with a Wang Electronic Calculator System (Model 380). These respective points of the standard curve were then retained by the electronic system for later use. As contrasted with the usual sigmoid-shaped curve of the standard values

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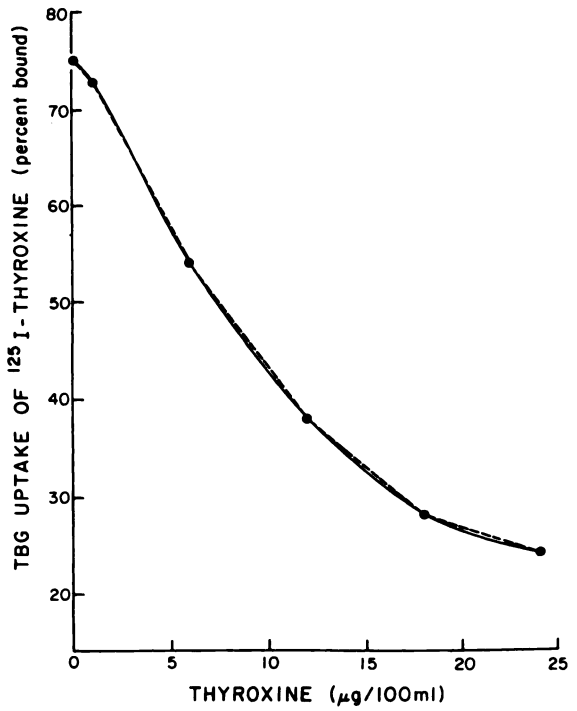

FIG. 1. Comparison of standard curve for obtaining T_4D obtained by visual fit (solid line) and by use of straight-line segments (dotted line).

obtained by the best visual construction, the computer treated the curve as a series of sequential straight-line segments connecting adjacent points (Fig. 1). Ordinate values for each unknown serum sample were then entered in a similar fashion. The computer applied this ordinate value to its appropriate straight-line segment, and the corresponding abscissa value was obtained and held in store as the serum thyroxine concentration (T_4D) of this sample. The computer was able to perform these tasks by means of a recycling program tape which "instructed" the calculator to perform the appropriate mathematical tasks and then store vital empiric derivations.

The RT_4, expressed as a ratio of a standard reference serum from a large pooled source of euthyroid serums, was then calculated from a similar TBG-resin system employing isotopic thyroxine (*10*). After entering the data necessary to obtain the percent TBG-bound radioactivity for the standard reference serum, the computer was programmed to calculate the absolute percent uptake for each unknown serum sample and then divide this value by the uptake of the standard reference serum to obtain and retain the RT_4 *ratio*. At this point, the mathematical product of each T_4D and its respective RT_4 ratio was obtained as the FTI-T_4.

To determine an appropriate diagnostic range of values for the FTI-T_4, criteria for delineating mathematic limits of this parameter were derived in conjunction with the established clinical thyroid diagnosis of the patients studied. Each category was created on the basis of the degree of mutual inclusion or exclusion of FTI-T_4 values of the hyperthyroid, hypothyroid and "normal" groups. FTI-T_4 values obtained by the computer and by previous manual methods were compared with each other and with previously described normal ranges (*11,12*). These latter ranges were delineated from ±3 s.d. of the mean FTI-T_4 values of 137 healthy, euthyroid blood bank donors. This range for the FTI-T_4 is 3.06–10.22. All statistic applications used standard methods (*12*).

RESULTS

Values of T_4D, RT_4, and FTI-T_4 obtained by computer were compared with similar values obtained through visual and manual calculations. Because the method for calculating RT_4 is identical in either case, these values were unchanged. T_4D and FTI-T_4 values, on the other hand, were slightly but not significantly different. T_4D values in the "normal," hypothyroid, and hyperthyroid categories were respectively 7.90 ± 2.16, 2.62 ± 1.10, and 14.90 ± 4.01 by computer calculation compared with 7.89 ± 2.19, 2.39 ± 1.09, and 15.07 ± 4.12 when determined manually. FTI-T_4 values in these same groups were 7.09 ± 1.97, 2.11 ± 1.05, and 19.62 ± 7.22 by computer analysis and 7.08 ± 1.98, 1.90 ± 1.00, and 19.82 ± 7.26 by manual means. The exclusion or inclusion of these values in a previously studied euthyroid range were not affected by these slight alterations in individual values. 93.8% of the "normal," but only 16.0% of the hypothyroid and 0.0% of the hyperthyroid values remained within ±3 s.d. of the mean FTI-T_4 derived from serum samples of blood bank donors. Ranges set for the FTI-T_4 for each thyroid diagnostic category are shown in Table 1 and Fig. 2. No hyperthyroid or hypothyroid FTI-T_4 values fell in the "normal" range of 4.56–10.45. Conversely, no "normal" values lay below the upper hypothyroid limit of 3.43 or above the lower hyperthyroid limit of 12.73. These two limits also greatly exceeded the respective limits of the 137 blood bank control serums. Within the FTI-T_4 range of 3.43–4.56, there were seven hypothyroid and 15 "normal" values (14.0 and 9.4% of the respective total values). Six (12.0%) of the hypothyroid values fell between 3.43 and 3.84 while only one hypothyroid value of 4.56 exceeded 3.84. On the other hand, five "normal" and five hyperthyroid FTI-T_4 values (3.1 and 7.1%, respectively) fell within the overlap range of 10.45–12.73 (Fig. 2).

A set of ranges for present and future FTI-T_4 determinations was thus incorporated in the computer

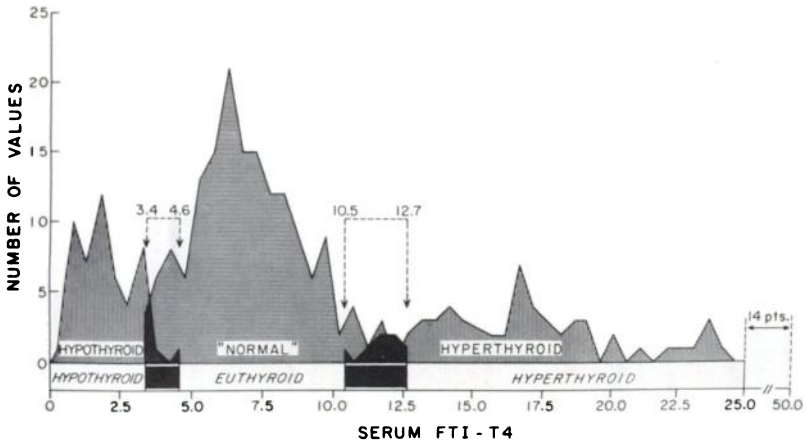

FIG. 2. Frequency distribution of FTI-T_4 values of hypothyroid, "normal," and hyperthyroid patients in this study.

program as follows: FTI-T_4 values less than 3.43 are considered hypothyroid; between 3.43 and 3.84 are borderline normal-hypothyroid; between 3.84 and 4.56 are probably euthyroid; between 4.56 and 10.45 are euthyroid; between 10.45 and 12.93 are borderline normal-hyperthyroid; and greater than 12.73 are hyperthyroid (Table 1). A sample computer run of a series of serum T_4D, RT_4, and calculated FTI-T_4 values and concomitant predicted diagnoses are shown in Fig. 3.

DISCUSSION

Measurement of the serum concentration of "free" thyroxine is currently considered to be the most useful laboratory reflection of the clinical thyrometabolic state of the individual (*15–19*). It has been shown, however, that direct measurements of this parameter are unnecessary under most clinical circumstances because an accurate estimate of the circulating levels of free thyroxine can be derived from two readily available laboratory tests of thyroid function; namely, the serum thyroxine concentration as determined by competitive binding analysis (T_4D) and one of the resin uptake tests (RT_3 or RT_4) (*11,12,20–24*). In this laboratory, an RT_4 procedure has been developed and used routinely to calculate the FTI-T_4. This FTI-T_4 is particularly advantageous for two distant reasons: (A) the FTI-T_4 provides a more distinct separation of euthyroid from hyperthyroid or hypothyroid values than does the FTI that uses the RT_3 (FTI-T_3) (*12*); and (B) the RT_4 can be performed in concert with the T_4D and thus, the FTI-T_4 can be obtained by a sequential, unified laboratory procedure using a single isotopic preparation of thyroxine. Because the FTI-T_4 provides meaningful and distinct separation of clinical disorders of thyroid function, it is particularly well suited to adaptation to a computer program for performance of tedious time-consuming and error-proof computations for these parameters and to render a predicted thyrometabolic diagnosis based upon derived ranges of the FTI-T_4 for each pathologic category. Results in this study support the utility and accuracy of applying a computer for these computations.

A relatively low-capacity computer-calculator is used in this laboratory to obtain the FTI-T_4 from the T_4D and RT_4 determinations. This task is accomplished by feeding into the input of the programmed electronic computer values for experimentally derived data necessary to obtain a standard curve for the T_4D determination. Sequential values are then entered for data from patient samples. As these lab-

TABLE 1. RANGES OF FTI-T_4 FOR DIAGNOSTIC DISCRIMINATION OF THYROID FUNCTION BY COMPUTER ANALYSIS

FTI-T_4 range	Hypothyroid*	"Normal"*	Hyperthyroid*	Computer diagnosis
< 3.43	86.0% (43/50)	0.0% (0/160)	0.0% (0/70)	Hypothyroid
3.43– 3.84	12.0% (6/50)	2.5% (4/160)	0.0% (0/70)	Borderline hypothyroid-euthyroid
3.84– 4.56	2.0% (1/50)	6.9% (11/160)	0.0% (0/70)	Probable euthyroid
4.56–10.45	0.0% (0/50)	87.5% (140/160)	0.0% (0/70)	Euthyroid
10.45–12.73	0.0% (0/50)	3.1% (5/160)	7.1% (5/70)	Borderline hyperthyroid-euthyroid
>12.73	0.0% (0/50)	0.0% (0/160)	92.9% (65/70)	Hyperthyroid

* Figures in parentheses represent the number of patients in that category over the total number of patients in the entire diagnostic group.

THE FOLLOWING ARE VALUES FOR T4D, RT4, FTI-T4, AND PREDICTED DIAGNOSTIC CATEGORIES FOR THE PATIENTS LISTED IN CONSECUTIVE NUMERICAL ORDER. THE DIAGNOSTIC CATEGORIES ARE DESIGNATED ACCORDING TO THE INCLUSION OF THE FTI-T4 IN ONE OF THE FOLLOWING RANGES: #1, (LESS THAN 3.43), HYPOTHYROID; #2, (3.43 - 3.84), BORDERLINE HYPOTHYROID-EUTHYROID; #3, (3.84 - 4.56), PROBABLE EUTHYROID; #4, (4.56 - 10.45), EUTHYROID; #5, (10.45 - 12.73), BORDERLINE HYPERTHYROID-EUTHYROID; #6, (GREATER THAN 12.73), HYPERTHYROID.

PATIENT NUMBER	T4D	RT4	FTI-T4	NUMBER OF DIAG. CATEGORY
1	6.81	1.02	6.94	4
2	13.53	.62	8.38	4
3	2.92	1.59	4.64	4
4	4.31	.82	3.53	2
5	5.24	.49	2.56	1
6	21.67	1.02	22.10	6
7	9.50	1.21	11.49	5
8	3.32	1.22	4.05	3
9	3.55	1.34	4.75	4

FIG. 3. Computer printout including values for T_4D, RT_4, and FTI-T_4 along with diagnostic assessment. The following clinical diagnoses apply respectively to the patients numbered one through nine: 1, euthyroid blood bank donor; 2, euthyroid pregnant patient; 3, euthyroid patient on therapeutic corticosteroids; 4, previously hypothyroid patient on 2 grains of desiccated thyroid replacement, daily; 5, hypothyroid patient on oral contraceptives; 6, pregnant patient with Graves' disease; 7, patient with thyrotoxicosis 6 weeks after initiation of oral antithyroid therapy; 8, euthyroid cardiac patient with congestive heart failure; and 9, euthyroid patient on therapeutic doses of diphenlyhydantoin.

oratory data for both standard and patient serums are performed in concert and samples are placed in a sequential manner in the gamma scintillation counter, data output from the counter printout can be fed directly into the computer input manually with a punch tape, or directly, by electronic coupling of the counter to the computer. Once data are entered into the programmed computer, the operational system functions automatically. It calculates the RT_4 by the same computational sequence used manually and at the same time, calculates the T_4D of the unknown samples from the T_4D standard curve. Statistical comparisons between values obtained by conventional and computer means showed no significant differences.

Empiric and clinically useful ranges were derived in the present study for computer categorization. These new diagnostic limits are based upon absolute inclusion or exclusion of FTI-T_4 values in diagnostic ranges obtained from large numbers of serum samples of patients with various thyrometabolic disorders. The euthyroid FTI-T_4 range of 4.56–10.45 thus correlates well with accepted T_4D ranges (*13*). This is not unexpected as the RT_4, which is multiplied by the T_4D to obtain the FTI-T_4, is expressed as a *ratio* of a standard reference serum. The hypothyroid-"normal" overlap is divided into two subcategories because of an isolated hypothyroid FTI-T_4 value of 4.56. In all practicality, however, FTI-T_4 values between 3.84 and 4.56 probably represent the euthyroid state. The relatively low percentage of "normal" and hyperthyroid values in the 10.45–12.73 range negate a similar subdivision here.

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