COST-BENEFIT ANALYSIS OF IN VITRO SCREENING TESTS OF THYROID FUNCTION

Determination of total serum thyroxine (T_4) by competitive protein binding (CPB) analysis first introduced in 1964 is regarded as the best single screening in vitro test of thyroid function and has replaced the PBI test for that purpose in many laboratories (*1*). However, the thyrometabolic state of the patient is not always reflected by total T_4 but is believed to be controlled by the free T_4 (FT_4) level which is dependent both on total T_4 and the concentration of the proteins which bind T_4. An index of FT_4 concentration may be estimated most simply and economically by performing both a T_4 (CPB) test and a test of protein-binding, such as the T_3 resin-uptake, on the same serum sample, and this is advocated by many laboratories, authorities, and commercial suppliers of T_4 and T_3 resin-uptake kits. We propose that the incidence of disease or drug-induced protein-binding abnormalities which result in misdiagnosis of the thyrometabolic state by the T_4 (CPB) test alone is so low that the FT_4 index obtained by performing both a T_4 and a T_3 test as routine screening tests of thyroid function cannot be justified.

The teaching hospital of the University of Florida College of Medicine is a 380-bed referral hospital with approximately 14,000 admissions and 120,000 outpatient visits yearly. Some 2,300 patients with suspected thyroid function abnormality were referred to the nuclear medicine laboratory in the period December 1969 through November 1971, during which time the single screening in vitro test for detecting possible hypothyroidism or hyperthyroidism was the T_4 (CPB) test. We recently reviewed the medical records of those patients and found that a euthyroid range of 2.7–9.3 μg% T_4I, which accounts for the non-normality of the distribution of euthyroid T_4I values, gave maximum discrimination between hypothyroid, euthyroid, and hyperthyroid patients (*2*). The distribution of T_4I values in eight categories obtained for this chosen euthyroid range is given in Table 1.

TABLE 1. DISTRIBUTION OF T_4I VALUES

Category	Number of patients	Patients with T_4I less than 2.7 μg%	Patients with T_4I greater than 9.3 μg%	Patients misclassified
Euthyroid	1,355	8	8	16
Hyperthyroid	32	0	31	1
Hypothyroid	47	47	0	0
Pregnancy	27	0	7	7
Estrogens	83	0	14	14
Androgens	5	1	0	1
Nephrosis	6	0	0	0
Dilantin	23	1	0	1
Totals	1,578	57	60	40

The great majority of elevated T_4 values due to elevated serum proteins are caused by pregnancy and estrogen administration. However, only 7 of 27 (26%) and 14 of 83 (17%) cases, respectively, had a T_4I value above the chosen euthyroid range. The great majority of decreased T_4 values due to decreased serum proteins are caused by androgen administration and nephrosis. Dilantin administration does not affect serum protein levels but does interfere with T_4 binding, resulting in a decreased T_4I value. However, only 2 of 34 (6%) cases in these categories had a T_4I value below the chosen euthyroid range. Knowledge of pregnancy or drug ingestion (estrogens, androgens, Dilantin) eliminated the necessity for a protein-binding test for those 23 patients. Thus only 17 patients (1% of the total) with T_4I values outside the euthyroid range needed a protein-binding test or further investigatory procedures such as an ^{131}I thyroid uptake and scan.

A recent survey of 17 academic nuclear medicine laboratories conducted by the Southeastern Chapter of the Society of Nuclear Medicine showed that only two in vitro thyroid function tests were performed in large numbers in 1971: 15,873 T_3 tests and 11,118 T_4 tests. In some laboratories the similar numbers of both tests suggest that both tests were performed routinely on patients with suspected thyroid function abnormality. Most laboratories charge about the same for a T_4 test and a T_3 test [e.g., $7 for a T_3 test and $7.75 for a T_4 by CPB test (*3*)], and hence routine use of both tests as a thyroid function screen increases patient cost by about 100% while increasing patient benefit (i.e., correct diagnosis) by 1%. We believe that this cost-benefit ratio cannot be defended and conclude that the T_4 (CPB) test as a single screening in vitro test provides sufficient diagnostic accuracy in assessment of thyroid function and that the additional T_3 resin-uptake test of protein binding to provide an FT_4 index is only indicated in those few cases where the low or high T_4I value (<2.7 μg% or >9.3 μg%, in our laboratory) cannot be explained by pregnancy or nephrosis or drug administration or is not accompanied by the appropriate clinical signs and symptoms of hypothyroidism or hyperthyroidism.

The discussion here has implied close cooperation between the referring physician and the specialist in nuclear medicine or a careful history (including drug administration) by the specialist. In laboratories where such close collaboration is not possible or the history cannot be easily obtained the T_3 resin-

uptake test or any other test to provide an FT_4 index [such as the newly developed effective thyroxine ratio (ETR) test] should be used routinely on patients with T_4I values outside the normal range. If such in vitro testing results in a normal value, the necessity for further confirmation of the hypothyroid or hyperthyroid state by the in vivo ^{131}I thyroid uptake test is eliminated. In our series such a sequence would have meant performing 117 T_3 or ETR tests on those 57 and 60 patients with T_4I values less than 2.7 μg% and greater than 9.3 μg%, respectively. The cost generated would have been 107% that of a T_4 test alone compared with the 200% cost of performing routine T_4 and T_3 or ETR tests on all patients.

In summary, we argue that a logical sequence of tests should be used in establishing the presence of hypothyroidism or hyperthyrodism, that the first test done be the T_4 test, followed, when the T_4I value is outside the normal range, by the T_3 resin-uptake test or other test providing an FT_4 index, and that further tests such as an ^{131}I thyroid uptake should be used as indicated in conjunction with a careful history and physical examination before treatment by drugs, surgery, or radioiodine.

VALERIE A. BROOKEMAN
CLYDE M. WILLIAMS
University of Florida
College of Medicine
Gainesville, Florida

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RADIOSTRONTIUM LOCALIZATION IN NORMAL LUNGS? OCCULT ASPERGILLOSIS VERSUS "APPARENTLY NORMAL" LUNGS

The observations regarding uptake of radiostrontium in lungs and other extraosseous tissues (*1*) are of considerable interest. Because of limitations of current diagnostic methods in pulmonary aspergillosis (*2*) and following up on the report by Ray, et al (*3*), ^{87m}Sr lung scans have been routinely used in the diagnosis of pulmonary aspergillosis at this center for the past 18 months. Radiostrontium consistently localizes in areas of radiological abnormality in various forms (allergic, invasive, and mycetoma) of pulmonary aspergillosis. To date strontium lung scans have been performed in 51 patients (18 with pulmonary aspergillosis), and the consistent reliability of this procedure in the diagnosis of pulmonary aspergillosis is impressive; these observations have been presented (*4*) and have been accepted for publication (*5*).

The report by Chaudhuri, et al (*6*) regarding radiostrontium localization in the radiologically normal lungs of a multiple myeloma patient without macroscopic or microscopic evidence of pulmonary calcification at autopsy (*1*) does not necessarily imply that the patient had "normal" lungs. This patient may have had occult pulmonary aspergillosis because this is the clinical setting where invasive aspergillosis occurs (*7*), and even at autopsy the diagnosis may be missed unless a determined histological search for Aspergillus is made using specific stains (*7,8*).

On the evidence presented, it is difficult to accept that radiostrontium localizes in normal human lungs, and this is certainly not the case in our experience.

N. ADISESHAN
Queensland Radium Institute
Brisbane, Queensland
Australia

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