

THE CASE FOR EUTHYROID HYPOMETABOLISM

BY MARSHALL GOLDBERG, M.D.*
WORCESTER, MASSACHUSETTS

THE existence of a certain group of patients whose clinical symptoms and low basal metabolic rates (BMR) suggest hypothyroidism, and yet, who derive no benefit from thyroxine therapy, has long been known (Kirk and Kvorning²⁵, Means³⁸). Such cases are generally regarded as having either a functional lowering of their metabolism secondary to malnutrition or psychoneurosis, or else, compromising the lower fraction of a normal distribution curve of basal metabolic rates. A rather constant feature of such patients has been the presence of anxiety states, labile emotions, and easy fatigability (Thurmon and Thompson⁵¹). Since therapeutic trials on L-thyroxine or desiccated thyroid were either ineffectual, or else, poorly tolerated, such psychodynamic symptoms were believed to be the cause of the low metabolism rather than the consequence of it. The isolation and identification of the potent, naturally occurring thyroid hormone, L-triiodothyronine (T-3), in the blood by Gross and Pitt-Rivers¹⁸, and in the thyroid gland by Roche, Lissitsky and Michel⁴³ in 1952, made available a second thyroid hormone for testing in patients with disturbed metabolic function. In 1955, a report by Kurland, Hamolsky and Freedberg²⁹ postulated the occurrence of a separate clinical syndrome of non-myxedematous hypometabolism based on long-term observations in 4 patients whose abnormally low BMR's, previously shown to be unresponsive to thyroxine, rose to nor-

mal levels on combined treatment of T-3 and thyroxine or high doses of T-3 alone. The above-mentioned authors suggested the theory that the hypometabolism in such patients was possibly on the basis of their failure to metabolize thyroxine to triiodothyronine at the cellular level. The original study by Kurland, Hamolsky and Freedberg²⁹ was subsequently followed by several reports (Fields¹², Frawley *et al.*¹⁴, Kupperman and Epstein²⁷, Levin³⁵, Morton⁴⁰, Tittle⁵², Weidenhamer⁵³) and editorials^{4,24} confirming or refuting the existence of non-myxedematous or euthyroid hypometabolism, the sum total of which settled neither the myth nor reality of the syndrome, but tended to compromise on the rarity of its occurrence. Despite the preponderance of endocrinologists stating that they were still searching for their first bona fide case of euthyroid hypometabolism, or disparaging the entire matter as a commercial invention of the pharmaceutical houses, the controversy was kept alive by the enthusiasm of general practitioners who seemed to be getting favorable results with T-3 in several of their chronically tired, thyroid-resistant cases, and the gynecologists and urologists struggling with their infertility problems.

As a military physician dealing with a fair number of both tense, tired patients and infertile couples, and with the belief that such features of military medicine as free laboratory facilities and efficient patient follow-up were

*Former medical officer, SHAPE Headquarters, Paris, France. Present address: The Memorial Hospital; Worcester, Mass.

advantageous to clinical research, a careful search for hypometabolic patients was begun in the winter of 1957. The following report is a summary of two years' observations and collected data on 32 patients believed to represent cases of euthyroid hypometabolism.

Materials and Methods. Approximately 500 patients, military personnel and their dependents, were evaluated by the methods to be described. Among this group, 32 patients (6.4%) were found to meet the diagnostic criteria for euthyroid hypometabolism listed in Table 1. The age of patients ranged from

minus 10%). 6) The electrometric recording of the Achilles tendon reflex by the Lawson kinemometer, done during each clinic visit (normal range: 150 to 240 milliseconds). Radio-iodine₁₃₁ uptakes were not done except to clarify a particular problem, such as, a PBI response which fell within the borderline range of a 1.0 to 1.5 μg . rise post-TSH.

Patients demonstrating both a normal baseline PBI and PBI-TSH response and a normal kinemometer tracing were excluded from this study. Patients believed to be cases of primary hypothyroidism as shown by an initial PBI below 4.0 μg . or a failure of the PBI to rise above 1.0 μg . post-TSH, or both, were likewise excluded from the hypometabolic group. The 32 patients displaying the

TABLE 1.—DIAGNOSTIC CRITERIA FOR EUTHYROID HYPOMETABOLISM

1. Symptom complex suggesting hypothyroidism and psychoneurosis.
2. Presumably normal thyroid (thyroxine) function as shown by a normal PBI and a normal rise in PBI post-TSH.
3. Objective evidence of deficient end-organ metabolism as shown by a low BMR and prolonged electrometric recording of the Achilles tendon reflex.
4. No response to placebo; equivocal or untoward response to desiccated thyroid in doses up to 300 mg. per day or toxicity.
5. A favorable response, both objectively and subjectively, to long term treatment with proper amounts of L-triiodothyronine.

15 to 45 years with an approximate sex ratio of 2:1: 20 females, 12 males. The period of clinical observation and treatment ranged from 5 to 19 months and averaged 10.5 months per patient, with an average of 15 clinical appointments during this period. The endocrine evaluation of these cases consisted of the following diagnostic procedures: 1) A detailed history and physical examination, including the completion of a questionnaire listing 52 symptoms known to be associated with the protean hypothyroid state. 2) Baseline protein-bound iodine determinations (PBI); the normal range for our laboratory being 4.0 to 8.0 μg . 3) A second PBI drawn 24 hours after the intramuscular injection of ten international units of a potent thyrotropic hormone preparation* (TSH): (a rise in PBI above 1.5 μg . following TSH was interpreted as evidence of normal thyroid (thyroxine) function; a rise less than 1.0 μg . post-TSH, to represent true hypothyroidism). 4) Serial serum cholesterol determinations before and after treatment with placebo, thyroid and T-3 (normal range: 150 to 250 mg.). 5) Serial BMR's done under oral barbiturate pre-medication (Hortling and Hiisi-Brummer²¹) (normal range: plus 10% to

combination of a normal TSH response in PBI and a prolonged (pseudomyotonic) tendon reflex tracing were then further investigated by serial BMRs, cholesterols, and kinemometer tracings while on the following medication given in sequence: a) a 4-week course of placebo therapy; b) a 4 to 8 week trial on desiccated thyroid, beginning with 120 mg. and increasing the dosage at 2-week intervals until either a 300 mg. level or thyroid intolerance was reached; c) finally, after thyroid had been discontinued for 10 days, a course of T-3 given in initial doses of 50 to 75 μg . per day and average maintenance doses of 75 to 150 μg . per day.

Results. Among approximately 500 patients screened, 32 cases of euthyroid hypometabolism were diagnosed; a percentage incidence of 6.4%. However, since a sizeable number of the psychoneurotic and suspected endocrine cases were referred to this clinic for study by the Area's physicians, this percentage incidence cannot be said to reflect the occurrence of euthyroid

*Thyréostimuline, generously supplied by the Endopanocrine Labs., Paris, France.

hypometabolism in the population at large. Table 3 lists the baseline results and changes secondary to treatment of the various thyroid-metabolic parameters employed in this study.

DIAGNOSTIC CRITERIA OF EUTHYROID HYPOMETABOLISM. 1) *A symptom complex and clinical appearance suggesting hypothyroidism in certain respects and psychoneurosis in others.* Table 2 compares the ten commonest complaints

of a group of 104 hypothyroid patients versus the 32 hypometabolic patients in this series as compiled by the returns of a questionnaire listing 52 symptoms known to occur in hypothyroidism, but, likewise, common to psychoneurosis. A feature shared by both groups was the multiplicity of complaints with fatigue, lethargy, gonadal dysfunction, and nervousness predominating. Certain differences in the

TABLE 2.—THE 10 MOST COMMON SYMPTOMS REPORTED BY A GROUP OF 104 HYPOTHYROID PATIENTS COMPARED WITH 32 EUTHYROID HYPOMETABOLIC PATIENTS.

Symptom	Hypothyroid		Symptom	Euthyroid Hypometabolic	
	Severe (3,4)*	Total (1-4)		Severe (3,4)	Total (1-4)
1. Fatigue- worse in a.m.	25%	56%	1. Fatigue- worse in a.m.	43%	84%
worse in p.m.	66%	80%	worse in p.m.	24%	66%
2. Lethargy	45%	92%	2. Irritability & Mood Swings.	42%	87%
3. Irritability & Mood Swings.	42%	94%	3. Lethargy	38%	81%
4. Pre-menstrual Tension	40%	81%	4. Decreased Libido	30%	67%
5. Myalgias & Arthralgias	37%	78%	5. Pre-menstrual Tension	28%	80%
6. Irregular Menses.	37%	72%	6. Gastro-intestinal Complaints.	26%	65%
7. Cold Intolerance	33%	88%	7. Seborrhea or Hair Loss.	20%	55%
8. Dry Skin	32%	80%	8. Palpitations	18%	45%
9. Paresthesias.	28%	86%	9. Myalgias & Arthralgias.	15%	50%
10. Brittle, Splitting Hair or Hair Loss.	23%	70%	10. Shortness of Breath.	12%	44%

*Symptoms were graded according to severity on an ascending scale of 1 (mildly troublesome) through 4 (chief complaint).

TABLE 3.—PRE- AND POST-TREATMENT LABORATORY RESULTS IN 32 EUTHYROID HYPOMETABOLIC PATIENTS

Therapy	N*	None	Average values and range			Thyroid	N	T-3
			N	Placebo	N			
PBI (μ g.)	35	5.4 (4.2-7.7)	—	—	—	—	—	
PBI rise post TSH	32	2.7 (1.6-4.0)	—	—	—	—	—	
BMR	41	-15% (-33%+7%)	32	-17.5% (-37%+5%)	35	-13% (-33%+11%)	104	-5% (-14%+18%)
S-D Interval Kinometer (millisec.)	44	255 (240-290)	64	255 (230-290)	134	250 (230-300)	258	200 (170-240)
Serum Chol- esterol	32	225 (080-350)	18	233 (160-370)	23	220 (165-360)	34	215 (140-345)

*N=number of determinations

symptomatology of the hypometabolic patient when compared to the hypothyroid patient were, however, apparent, such as: fatigue worse at the beginning of the day rather than in the late afternoon or evening; oligomenorrhea, rather than met-menorrhagia; an oily, seborrheic condition of the skin and scalp rather than thick, dry skin; hypotension (oftentimes postural) instead of the tendency for hypertension reported as common in hypothyroidism (Sheedy and Lienhard⁴⁷); normal or excessive sweating, rather than decreased sweating.

Pre-treatment measurement of body weight fell within the accepted range of normal in less than half of the hypometabolic group: 14 of 32 patients being 20% or more overweight, and 4 being 20% underweight. Two of the underweight patients were, in fact, suspected initially of being hyperthyroid until the report of their BMRs, both below minus 20%, necessitated a hasty reversal of opinion.

Findings on physical examinations were unremarkable, with the exception of eliciting the "hung-up" Achilles reflex *clinically* in several patients. Thyroid enlargement beyond slight fullness to the isthmus or thyroid nodules was distinctly uncommon, each abnormality being found only once in this series of cases.

2) *Presumably normal thyroid (thyroxine) function as shown by normal baseline PBIs and a significant rise in PBI post-TSH.* Although the TSH test as employed by Jeffries *et al.* in the diagnosis of equivocal hypothyroidism²² and low thyroid reserve²³ employs both the radio-iodine₁₃₁ uptake and PBI response to TSH, the I₁₃₁ uptake was omitted here of necessity. The response of the PBI alone to TSH is, however, believed to be a valid measure of thyroid responsiveness and thyroid reserve for the following reasons:

a) the ability of the gland to respond to exogenous thyrotropin by the formation and release of active hormone (measured in the serum as PBI) is logically a more accurate test of thyroid potential than is the measurement of the gland's avidity for iodine. b) According to Levy³⁶, the experience of Jeffries' group with over 1,000 TSH tests, and our own experience with 200 or more tests using the PBI alone¹⁵, clearly shows that the patient whose PBI rises 1.5 $\mu\text{g.}$ or more following TSH is rarely hypothyroid at that time; in contrast, the patient whose PBI fails to rise above 1.0 $\mu\text{g.}$ post-TSH usually responds to thyroid hormone replacement, both objectively (BMR, PBI, cholesterol, and others), and subjectively, and such improvement is maintained on physiological dosages. c) Among 70 patients found to have a normal PBI, and yet, a prolonged kinemometer tracing and low BMR, an adequate PBI-TSH response was seen in only 32 patients (the ones considered here to be euthyroid hypometabolic); the remaining 38 patients were later proved to be unequivocally hypothyroid, the false normal PBIs being secondary to iodine contamination from medications containing iodine or Roentgen-ray contrast media. Twenty-two of these 38 patients originally started on T-3 in view of the possibility that they might be hypometabolic rather than hypothyroid, later responded to equivalent amounts of desiccated thyroid regardless of a suggestive history or initial response. It is worth emphasizing that *the inadequate PBI response to a TSH preparation of known potency has reduced considerably the number of patients whose initial PBIs were reported as normal or borderline low and who might therefore have been included in the hypometabolic category.*

3) *Objective evidence of deficient end-organ metabolism as shown by*

BMR and electrometric recording of the ankle reflex. Although the electrometric recording of the abnormal tendon response in myxedema patients was first reported in the literature by Lambert in 1951³¹, the simplicity and economy of the Lawson kinemometer makes it a utilitarian device for use in the clinic. Previous reports by Lawson have demonstrated the kinemometer to be 94% accurate in distinguishing between euthyroidism and even the milder degrees of hypothyroidism in

The *initial* BMR values in these 32 cases fell within the following ranges:
 —35% to —20%, 12 patients
 —20% to —10%, 5 patients
 —10% to 0%, 13 patients
 0% to +10%, 2 patients

Thus, it can be seen that little more than half of this group displayed low BMRs on initial testing. Subsequent BMRs in the remaining 15 patients, usually run on 2 or more consecutive mornings, revealed at least one BMR of —10% or below in all cases. A tabu-

TABLE 4.—A COMPARISON OF BMRs AND KINEMOMETER TRACINGS RECORDED ON 3 CONSECUTIVE DAYS ON 10 EUTHYROID HYPOMETABOLIC PATIENTS.

Patient	BMR (normal —10% to +10%)				Kinemometer (normal 150–240 millisecc.)			
	Day 1.	2.	3.	Change	Day 1.	2.	3.	Change.
K.K.	—6	—24	—22	—18%	250	250	250	0 millisecc.
A.Me.	—19	—21	—23	—4%	260	250	260	0 “
B.G.	+4	—5	—12	—16%	260	260	270	10 “
H.K.	—15	—14	—18	—3%	80	280	280	0 “
C.C.	—8	—19	—26	—18%	50	240	250	0 “
H.M.	—3	—18	—19	—16%	60	260	260	0 “
L.G.	—22	—25	—24	—2%	80	280	280	0 “
I.G.	+12	—1	—14	—26%	70	260	260	10 “
J.K.	—10	—15	—17	—7%	40	250	250	10 “

over 3,000 patients tested (Lawson^{33,34}). The fact that the standard BMR procedure requires complete relaxation on the part of the patient coupled with the fact that the typical hypometabolic patient is a tense, anxious individual, oftentimes leads to a false elevation of the BMR, particularly if it is the patient's first experience with the BMR procedure. In contrast, the contraction phase (*S-D interval*) of the Achilles reflex prolonged beyond the upper limits of normal of 240 milliseconds has been a constant finding in this series of 32 euthyroid hypometabolic cases, and is considered to be the most reliable criterion in screening such patients.

lation of BMRs and kinemometer tracings recording on 3 consecutive days in 10 “hypometabolic” patients is presented in Table 4. The superior accuracy of the kinemometer tracing in comparison to the BMR in the screening of patients for hypometabolism is evident, for although the *S-D interval* of the reflex varied less than 10 milliseconds, the BMR in 7 out of the 10 patients dropped significantly on each succeeding day. Elevated serum cholesterols were found in 8 (25%) patients, and responded significantly to T-3 therapy in 7 of the 8 patients.

That the contraction phase of the reflex is prolonged in both hypothyroid-

ism and euthyroid hypometabolism, suggests that the reactivity of the reflex best correlates with the peripheral or end-organ action of the thyroid hormones rather than the release of active hormone by the gland itself. The reflex tracing is thus similar to BMR and cholesterol, with the added advantage of being unaffected by emotional stimuli which might alter the BMR, or systemic factors, such as hepatic or biliary diseases which might influence the total cholesterol.

4. *No response to placebo; equivocal or untoward response to desiccated thyroid given in doses up to 300 mg. per day or intolerance.* Upon completion of the initial clinical and laboratory studies, all patients in this series were given a 4-week trial on placebo therapy. This procedure was followed in lieu of a double blind investigation because of the fact that the kinemometer tracing, repeated each clinic visit, would readily reveal (through changes in the baseline *S-D interval*) which patients were receiving active hormone medication. That the overall response of the hypometabolic patient to placebos was poor, was not surprising in view of the fact that these patients had previously been treated with numerous symptomatic drugs. At least two-thirds of this group had been taking, or were currently taking, one or more of the various tranquilizers. Weaning these patients off both tranquilizers and amphetamines proved difficult, but essential, as it is suspected that certain tranquilizer agents inhibit the action of exogenous T-3.

Following placebos, patients were started on 120 mg. of desiccated thyroid and the dosage increased by increments of 60 mg. at 2-week intervals until either objective improvement or symptoms of overdosage resulted. It was a curious finding that less than

half, or 15, of the 32 euthyroid hypometabolic patients could tolerate more than 120 mg. of whole thyroid without toxicity despite the fact that they later proved to be able to tolerate equivalent amounts or more of T-3*. Only 4 patients reached the 300 mg. level without intolerance. Among 10 patients showing an initial response to thyroid with symptomatic improvement and rise in BMR, such improvement was short-lived: both symptoms and BMR returning to pre-treatment states within 3 to 5 weeks, despite continuance of thyroid medication.

5) *A favorable response, objectively and subjectively, to long-term treatment with adequate amounts of T-3.* The criteria used to judge unequivocal improvement on T-3 were the following: a) alleviation of clinical signs and symptoms secondary to hypometabolism, such as: nervousness, fatigue, genital dysfunction, and the like; b) return to within normal limits of the kinemometer tracing when the proper daily maintenance level of T-3 was reached; c) elevation of BMR to within normal limits, and *maintenance of a normal BMR over a minimum follow-up period of 5 months.*

The above objectives were reached in these cases with an average daily dose of 112 μ g. T-3 and a dosage range of 75 to 150 μ g. Patients were followed at bi-weekly intervals and T-3 dosages adjusted according to the *S-D interval* of the kinemometer, the optimum being a contraction phase approximating 200 milliseconds. A noteworthy difference was observed in the response of the hypothyroid patient versus the hypometabolic patient to initial treatment with 75 μ g. T-3, in that the average hypothyroid patient improved rapidly, within 2 to 5 days, while the hypometabolic patient required 2 to 4 weeks and oftentimes, a higher dos-

*Dosage equivalents used in this series: 60 mg. thyroid = 37 μ g. T-3.

age of T-3 before either symptomatic improvement or shortening of the S-D interval was noted. A time lag between the onset of T-3 therapy and its effect in raising the low BMRs in euthyroid hypometabolic patients has likewise been noted by Kurland²⁸, but remains unexplained.

The importance of weaning hypometabolic patients from tranquilizer drugs before instituting T-3 therapy, and the necessity of insuring that the patient receives adequate amounts of T-3, are illustrated in the following 2 case histories of patients outside this present series.

Case Reports. CASE 1. Mrs. L., a 42-year-old white woman, was referred to the endocrine clinic because of severe depression and myxedemous facial appearance. Symptoms of depressive reaction and generalized apathy had progressed during the previous 4 years despite long-term psychotherapy and electroshock treatment on one occasion. During her initial interview, Mrs. L. admitted taking tranquilizers and sedatives, but stated that she took them only sporadically.

The following laboratory data indicated euthyroid hypometabolism: Initial PBI, 4.0 $\mu\text{g.}$; PBI post-TSH, 8.0 $\mu\text{g.}$; BMR, minus 37%; cholesterol, 300 mg.; S-D interval, 280 millisecc.

The patient was started on 75 $\mu\text{g.}$ daily of T-3 and raised to 100 $\mu\text{g.}$ within one week. Over the next 3 weeks, the dosage of T-3 was raised to 175 $\mu\text{g.}$ per day without noticeable improvement. Repeat laboratory tests while patient continued on 175 $\mu\text{g.}$ were essentially unchanged: BMR, minus 33; cholesterol, 320 mg.; and S-D interval, 270 millisecc. Puzzled by the apparent lack of response, the patient's use of tranquilizers was elicited in more detail. This revealed that she was actually taking seven or eight 500 mg. Placidyl (ethchlorvynol) tablets per day in addition to three or four 25 mg. chlorpromazine tablets. Within 3 days after discontinuing tranquilizers completely, the patient now stated that she looked and felt better than she had in years. Her S-D interval was now 200 millisecc. and a repeat cholesterol, 190 mg. The daily dosage of 175 $\mu\text{g.}$ T-3 was continued until 48 hours later, at which time the patient complained of restlessness, tremor, excessive sweating, palpitations, and other symptoms of T-3 overdosage. Her S-D

interval was now 140 millisecc. In view of her previous resistance to T-3 while on tranquilizers, the patient was given 2.5 mg. of intramuscular reserpine and carefully observed. Approximately 8 hours later, the patient's hypermetabolic symptoms had abated, her pulse rate had decreased from 120 to 90 beats per minute, and her S-D interval had lengthened to 180 millisecc.

Patient was subsequently regulated on 125 $\mu\text{g.}$ T-3 daily and has done remarkably well.

COMMENT. The relationship between thyroid function and the action of certain tranquilizer agents, reserpine in particular, has now been the subject of several reports (Canary *et al.*⁶, De Felice⁸, DeFelice, Smith and Dearborn⁹, Goodman¹⁶, Kuschke and Gruner³⁰, Mayer, Kelly and Morton³⁷). Both the observations of Canary⁶ in human patients with thyrotoxicosis and DeFelice in rats⁸, suggest that reserpine's amelioration of the hypermetabolism brought about by excess circulating thyroid hormones may conceivably involve inhibition of peripheral utilization of thyroid hormones, possibly by blocking the potentiating effects of the adrenal medullary hormones (Brewster *et al.*⁵). Since the initial experience with Mrs. L., parenteral reserpine has been successfully employed in 3 other patients who were inadvertently overdosed with T-3, with both pulse rates and kinemometer tracings returning to normal in a matter of hours. It would thus appear that parenteral reserpine is an effective means to "back-titrate" the occasional patient, particularly the cardiac patient, made hypermetabolic by exogenous thyroid hormones.

CASE 2. Colonel H., a 35-year-old white man, was referred for endocrine evaluation of impotency of one year's duration. Other symptoms included: hair loss, morning fatigue, nervousness and feelings of inadequacy, lethargy and chest-wall myalgias. Laboratory data was reported as follows: Initial PBI, 5.2 $\mu\text{g.}$; PBI post-TSH, 7.5 $\mu\text{g.}$; BMR, minus 15%; cholesterol, 240 mg.; S-D interval, 250 millisecc. Patient was started on 50 $\mu\text{g.}$ T-3

daily, and instructed to return to the clinic in one week. He was unable to keep this appointment and was next seen one month later, at which time he complained of increased nervousness, palpitations, muscle cramps, insomnia, constant fatigue and a general listlessness. A kinemometer tracing showed a lengthening of the S-D interval to 270 millise., despite his taking 50 μg . of T-3 daily. BMR was now minus 24%.

T-3 therapy was increased to 75 μg . daily for one week and then to 100 μg . The latter dosage was maintained for 2 weeks at which time the S-D interval shortened to 230 millise., and then increased to 125 μg . per day. On this dosage the patient noticed considerable improvement in both his sexual performance and emotional stability. His S-D interval has stabilized at 200 millise. and his BMR has ranged between minus 5% and zero over a 9-month period of follow-up.

COMMENT. A great practical advantage of the kinemometer over the standard BMR or PBI in following patients treated with thyroid hormones is that an estimate of metabolic status can be obtained while the patient is still in the doctor's office and thyroid medication adjusted without delay. Although initiating therapy with small increments of T-3 ranging from 12 to 25 μg . per day has been generally recommended by previous authors, a worsening of the patient's hypometabolic state in the early days of treatment with this regimen has been common enough and troublesome enough (as in the case of Colonel H.) that it is our preferred practice to start uncomplicated cases in the younger age groups on 75 μg daily and raise this to 100 μg . of T-3 within one to 2 weeks. The paradoxical worsening of the hypometabolic patient on the lower dosage schedules of T-3 has likewise been observed by Adelman². Although a precise explanation for this phenomenon is not known, it is conceivable that T-3 in dosages of 12 to 60 μg . may profoundly suppress the endogenous production of thyroxine via inhibition of

TSH release. Studies by Starr, Snipes and Liebhold-Schuek⁵⁰ and McConahey and Owen³⁹ have demonstrated marked suppression of RAI_{131} uptake in euthyroid individuals given small amounts of T-3, ranging from 8.8 to 35 μg . Thus treatment of a patient with 50 μg . T-3 daily (an amount which in itself is insufficient to maintain a normal BMR in an athyreotic individual), may conceivably, by inhibiting endogenous thyroxine release, make the patient more hypometabolic. Whether the mechanism by which T-3 suppresses TSH is more sensitive in the hypometabolic patient than in the normal is presently unknown, but the potency of T-3 in suppressing both TSH and RAI_{131} uptake is well established (Halmi *et al.*¹⁹). For this reason, T-3 therapy is logically given with the aim of either completely replacing endogenous thyroxine as the circulating thyroid hormone, or else, in dosages insufficient to suppress TSH, as reflected roughly in the radio-iodine uptake. Since the latter amount is variable and therefore difficult to approximate in any given case, the former procedure is the one that is recommended.

The use of T-3 in an investigative capacity in well over 200 patients has shown this substance to be remarkably free of untoward reactions. Aside from symptoms of overdosage, the only side effects noted were transient swelling of the salivary glands in 2 patients. The safety of T-3 when properly administered is in marked contrast to the reported incidence of sensitivity reactions to the various tranquilizer agents (Shaw and Felts⁴⁶).

Discussion. The skepticism which has generally arisen over the alleged or actual existence of euthyroid hypometabolism is based on several reasonable objections. With the noteworthy exception of the original study by Kurland, Hamolsky and Freedberg,

based on carefully conducted long-term observations, the majority of case reports concerning euthyroid hypometabolism have lacked the support of convincing laboratory data. Despite the fact that almost all present-day techniques which measure the functional capacity of the thyroid gland itself are within normal limits in the hypometabolic patient, such tests are, nevertheless, necessary to separate cases of euthyroid hypometabolism from those of actual hypothyroidism. The BMR, which in theory should be significantly low, is oftentimes falsely elevated in the typically tense, anxious hypometabolic patient. The kinemometer offers the advantage of being consistent in value when repeated several times in the same patient (Lawson³³). Double-blind studies alternating T-3, desiccated thyroid, and placebos, encounter the difficulty of using predetermined amounts of T-3 rather than dosages individually adjusted by objectively measured metabolic response. The dosages used in a double blind evaluation can be a crucial factor as was shown in the study carried out in Great Britain to determine the relative effectiveness of aspirin versus cortisone in the treatment of acute rheumatic fever (Robinson⁴²). Likewise, the interpretation of a therapeutic trial based on subjective response alone is fraught with error. Not only is a positive response to T-3 inconclusive evidence of hypometabolism rather than placebo effect, but a negative response does not rule out a true hypometabolic state improperly or inadequately treated. If a therapeutic trial does not extend beyond the time lag oftentimes seen in the hypometabolic patient before a response to T-3 is forthcoming, or if the patient is taking tranquilizers such as reserpine at the same time, results can be quite equivocal. Furthermore, in the absence of ob-

jective means by which to spot-check the patient's metabolic response, such as the BMR or kinemometer, the nervousness produced by emotional stress or pre-menstrual tension can easily be confused with T-3 overdosage.

During the past year, two reports have been published which utilized the double blind method in studying patients suspected of euthyroid hypometabolism; both of them, failing to confirm the existence of the syndrome by the methods employed. The first such investigation, by Levin³⁵, found no significant difference in the response to T-3, as compared to placebo and L-thyroxine, in 6 patients studied. A maximum dosage of 75 μ g. of T-3 daily was prescribed and this was taken for a period of 2 weeks by 2 patients and 4 weeks by 4 patients; the study being concluded after a total period of 4 weeks on each of the three medications. However, since it has been our usual experience that the majority of hypometabolic patients usually require 2 to 3 weeks on 100 μ g. or more of T-3 before either objective or subjective improvement is forthcoming, the failure of Levin's patients to show a positive response to this type of T-3 therapy is not unexpected.

A second study of suspected hypometabolic patients was reported by Sikkema⁴⁸, in which 20 patients with low BMRs (averaging -16%) and normal PBI values, showed no significant change in either symptoms or BMR when treated with placebos or triiodothyronine for a period of 6 weeks. The daily dosage of T-3 employed in individual cases is not stated, although the dosage range for the group was said to be from 62.5 to 150 μ g. Among the patients responding favorably to T-3, an identical response was observed after T-3 therapy had been discontinued and the patients placed on an equivalent amount of desiccated thy-

roid. Sikkema further states that, among 73 patients considered by her to be hypothyroid, initial PBI determinations were carried out in only 28 cases; 21 of the 28 PBI values falling within the normal range. Based on this, Sikkema concludes that the BMR is superior to the PBI determination as a screening test for hypothyroidism.

This raises the objection that, since the PBI values reported by Sikkema's laboratory are normal in the majority of her hypothyroid patients as well as in the patients suspected of euthyroid hypometabolism, this diagnostic procedure cannot be justifiably employed to separate cases into euthyroid, hypothyroid or hypometabolic categories for the purpose of double-blind investigations. Patients with true hypothyroidism would naturally be expected to respond equally well to equivalent amounts of T-3 or whole thyroid. The question is thus raised as to whether or not the 20 patients suspected of being hypometabolic by Sikkema were actually hypothyroid. It was with this important distinction in mind that TSH tests were carried out on the 32 patients comprising this present study.

The theory originally proposed by several authors to account for the occurrence of euthyroid hypometabolism: namely, that such patients are unable to deiodinate thyroxine to T-3, its peripherally active metabolite, has not met with general acceptance. Based on preliminary data by Pitt-Rivers, Stanbury, and Rapp⁴¹, the above-mentioned theory seemed an attractive one, but rested on the premise that the conversion of thyroxine to T-3 was a natural pathway for the metabolism of the thyroid hormones. Neither Roche and Michel⁴⁴, working with *in vivo* systems, nor Lassiter and Stanbury³², who attempted to reduplicate the original experiments of Pitt-Rivers *et al.*, could confirm the conversion of thy-

roxine to T-3 *in vivo*, although there is some documentation that *in vitro* slices of kidney, liver, heart and skeletal muscle are able to deiodinate small amounts of thyroxine to T-3 (Albright and Larson³). The radio-active labeled T-3 recovered in the plasma of humans and animals by various investigators (Roche and Michel⁴⁵, Starr, Snipes and Liebhold-Schuek⁵⁰) is believed to be formed and released directly from the thyroid gland itself.

The failure to find abnormalities in either the thyroidal iodine trap, the formation and release of thyroxine, binding mechanisms which transport thyroid hormones through the plasma, or the TSH response, raises the possibility that the pathophysiology underlying the hypometabolic state may involve neuro-endocrine systems outside the thyroid gland itself; that thyroid function is only secondarily affected, as in hypopituitary myxedema, resulting in an inhibition of the formation and release of T-3, or else, an exhaustion of thyroidal stores of T-3. In short, rather than being a thyroid disease at all, euthyroid hypometabolism may conceivably be a state of T-3 deficiency secondary to dysfunction at the cortico-hypothalamic level.

From the experimental studies of Greer¹⁷, Harris and Woods²⁰ and many others (D'Angelo⁷, Yamada and Greer⁵⁴), the hypothalamus is known to exert a regulating influence on many phases of thyroid-pituitary function; an intact hypothalamus being essential to the proper elaboration of the thyroid hormones. Clinically, the typical hypometabolic patient bears close resemblance to the cases categorized by Starr as hypothalamic hypothyroidism several years ago⁴⁹. The following evidence can be cited to suggest relative gonadal failure: amenorrhea or oligomenorrhea (in contrast to the metmenorrhagia usually encountered in

the hypothyroid female), anovulation and infertility, occasional uterine hypoplasia, impotency or frigidity, low or low normal sperm counts with depressed sperm motility, and the like.

Implicating mild adrenal dysfunction, one finds: easy fatiguability, postural hypotension, functional hypoglycemia and, on occasion, low urinary 17-ketosteroids. To date, three hypometabolic women have been found to have total urinary 17-ketosteroids below 3 mg. per 24 hours; the presenting complaints in 2 of the 3 being infertility. A significant rise in 17-ketosteroids to levels of 6.6, 7.3 and 9.1 mg. per 24 hours was observed in these 3 patients consequent to T-3 therapy. An investigation of 17-hydroxycorticoid excretion in 7 hypometabolic patients revealed normal values throughout. Kupperman and Epstein²⁷ have reported flat oral glucose tolerance tests to be a frequent finding in euthyroid hypometabolic patients. Although not carried out as a routine, glucose tolerance tests were performed in 9 patients in this series and judged to be flat in 4.

In both mannerisms and appearance, the hypometabolic patient bears an almost indistinguishable resemblance to the true psychoneurotic; the clinical distinction being possible only by the presence of an abnormal Achilles reflex tracing. That such a distinction is worth making at all, is upheld by the overall improvement observed by this author in the great majority of euthyroid hypometabolic cases when treated with T-3. In contrast to this, stands the fate of the true neurotic: dependence on tranquilizers or expensive, prolonged psycho-therapy.

An important aspect of the relationship between euthyroid hypometabolism and psychodynamic symptoms and one which remains as yet undecided, concerns the sequence of their dual occurrence: namely, does the hypometabolic state precede the overt neu-

rosis, or rather, does the psychodynamics of the neurosis itself disturb neuro-endocrine function sufficiently to lead to T-3 deficiency and euthyroid hypometabolism? An intriguing study by Kissin *et al.*²⁶ attempted to show the presence of parasympathetic overactivity and mild pan-endocrine hypofunction in a series of 19 patients with "psychic fatigue"—usually severe anxiety states or depressive reactions; 65% of which, likewise, had low BMRs. Without venturing into a discussion of cause-and-effect mechanisms, Kissin's study suggested that the concomitant presence of panendocrine hypofunction and severe psychoneurosis is not uncommon when endocrine studies are pursued in such patients.

Though it has been long known that epinephrine potentiates the metabolic response of thyroid hormones at the peripheral level (Ellis¹⁰), recent experiments by Ackerman and Arons¹ suggest a direct effect of epinephrine and norepinephrine on the acute release of thyroxine and triiodothyronine by the thyroid gland. Radio-chromatographic results in two experiments were particularly interesting in that they demonstrated release of both labeled thyroxine and T-3 following epinephrine administration, but release of thyroxine alone following TSH. The possibility is raised by these authors that the thyroid may play a much more significant role in the stress reaction than was previously realized, and that the adrenal medullary hormones released during stress may, in turn, stimulate the thyroid's release of T-3 and thyroxine. If, in the future, it can be shown that T-3 is preferentially released by the thyroid during stress, particularly emotional stress, then it is conceivable that hypometabolism could result from a stress depletion of T-3 reserves, rather than an actual inhibition of T-3 release.

The following case history of a pa-

tient with anorexia nervosa is cited as a possible example of cortico-hypothalamic depression of basal metabolism reversible by therapy with T-3:

Case Report. Mrs. C.S., a 30-year-old white woman, was first seen in mid-July, 1958, following hospitalization for what appeared to be a classical picture of anorexia nervosa. The patient first experienced the gradual onset of fatigue and apathy following the uncomplicated pregnancy and birth of her first child in March, 1958. A BMR taken in early June was minus 25%. The patient's weight at that time was 130 lbs., her normal weight. Her PBI was reported as 5.5 μ g. The patient was started on 120 mg. desiccated thyroid by her physician and was being maintained on 180 mg. per day when she progressed to full-blown anorexia nervosa. When hospitalized in July, her body weight had decreased to 98 lbs. and her BMR was then minus 33%. Increasing the thyroid to 300 mg. per day, although raising her PBI to 8.2 μ g., had only slight effect on her BMR, raising it to minus 30%. Additional endocrine studies showed a low level of urinary gonadotropins, decreased cornification on vaginal smear, normal ACTH response of 17 keto- and hydroxycorticoids, and a normal TSH response: the PBI rising from 7.8 to 10.4 μ g. post-TSH.

In early August, after thyroid medication had been withdrawn for 10 days, the patient was started on 75 μ g. T-3 daily. One week later, while on 100 μ g. T-3, her BMR had risen to minus 20%. T-3 therapy was subsequently raised to 150 μ g. per day and maintained at that dosage for 2 months, the BMR varying from minus 14% to minus 3%. Concomitant with the rise in BMR, the patient became more responsive to psychotherapy. At the time of her hospital discharge in September, 1958, her weight had increased to 120 lbs. and she seemed capable of returning to full-time duty as a housewife. She is presently being maintained on 125 μ g. T-3 and her BMR has remained above minus 10 on repeated testings.

COMMENT. Although anorexia nervosa is generally considered to be basically a non-endocrine disorder, two relatively constant findings have been low urinary gonadotropins and low BMRs (Emanuel¹¹). The latter is inconsistently affected by physiological amounts of whole thyroid and usually

attributed to malnutrition. In the case of C.S., however, a BMR of minus 25% was documented several weeks prior to any significant weight loss. Furthermore, her low BMR, unaffected as it was by 180 to 300 mg. of desiccated thyroid, responded promptly to T-3 and was maintained within normal limits, thereafter. Whether the above-mentioned case represents an actual instance of hypothalamic suppression of both gonadotropin and metabolic (T-3) function, with thyroid (thyroxine) and adrenal function being spared, or whether, in fact, T-3 deficiency is typical for anorexia nervosa cases in general, is certainly debatable. A second anorexia patient treated in a nearby hospital with T-3 and a case reported by Flack¹³ seemed to respond in similar fashion, although the full details on these patients are lacking.

Conclusions. On the basis of long-term observations made on the 32 cases comprising this report, the syndrome of euthyroid hypometabolism is believed to exist as a distinct clinical entity, although its etiology and true incidence among the population at large remains undetermined. Such patients are oftentimes mistaken for psychoneurotics and are thus analyzed, tranquilized or merely despised, with haphazard results. Treatment of such cases with T-3 is not always a cure-unto-itself, however, for a neurosis which either antedated the hypometabolic state or became rooted in it is not likely to respond as quickly as a low basal metabolism. T-3 is, nevertheless, proper and effective supportive therapy and may further the ultimate response of the hypometabolic patient to needed psychotherapy. Several factors believed to have influenced and perhaps concentrated the present series of cases are worth reiterating. The hypometabolic patient, with his multiplicity of complaints, is prone to congregate

wherever free medical care is offered, such as at an Army medical dispensary. It is highly likely that such patients will be channeled towards the psychiatric rather than endocrine clinic unless, as was the case during the first year of this study, no psychiatric treatment facilities are available. The psychiatric outpatient clinic is thus recommended as being fertile ground for the endocrinologist seeking cases of euthyroid hypometabolism. As a corollary: patients referred for psychiatric aid can and should be easily screened for hypothyroidism or hypometabolism by the kinemometer. An S-D interval prolonged beyond normal limits is an objective finding uninfluenced by doctor-patient relationship or the power of suggestion, and obviates, to a great extent, the necessity of performing double-blind studies. As a parameter of metabolic status and response to thyroid medication, the kinemometer has proved superior to the conventional BMR. Since no one has yet improvised a laboratory test to establish a positive diagnosis of psychoneurosis, the kinemometer tracing can, at least, separate the psychoneurotics with normal thyroid-metabolic function from the neurotics or non-neurotics with concomitant hypometabolism. The overall response of the euthyroid hypometabolic cases to optimum doses of T-3 as *sole* medical treatment was impressive and sufficient to render the patient relatively asymptomatic in 23 of 32 cases. The remaining 9 patients showed physical improvement, but required short-term psychotherapy to help them cope with their everyday emotional problems.

Finally, it is the author's belief that the favorable results brought about by T-3 therapy in these patients was not a placebo-type response. Insofar as possible, objective, and not subjective, criteria were used to judge improve-

ment; the primary goals being a normal reflex pattern and BMR, rather than alleviation of particular symptoms. Since Lawson has convincingly shown that the kinemometer is affected only rarely by medical conditions other than hypothyroidism or hypometabolism (Lawson³³), and very few drugs outside of the thyroid hormone, it is deemed unlikely that the changes noted in the S-D interval during T-3 therapy resulted from anything other than a raised metabolism. Lastly, considering that the majority of these patients had taken various symptomatic medications in the past, were, in fact, inveterate pill-takers, and that these patients were informed that they would probably require lifetime maintenance on T-3 therapy, it is believed unlikely that their general improvement was artifactual.

Summary. Among approximately 500 patients screened for the controversial syndrome of euthyroid hypometabolism, 32 individuals (6.4%) were found who met the five diagnostic criteria for this disorder proposed by the author. Such patients showed normal PBI values and a normal rise in PBI after TSH, and yet, BMRs and kinemometer tracings of the Achilles reflex in the hypothyroid-hypometabolic range. Although unresponsive to placebos or desiccated thyroid, such patients responded favorably, both objectively and subjectively, to therapy with L-triiodothyronine. Dosages of L-triiodothyronine ranged from 75 to 150 μg . per day and averaged 112 μg . per patient. A paradoxical worsening of hypometabolic symptoms when patients were given insufficient amounts of L-triiodothyronine, and the necessity of weaning such patients off tranquilizers prior to initiating therapy is discussed. Although the true etiology and incidence of euthyroid hypometab-

olism remain undetermined, it is believed that this syndrome does, in all likelihood, exist, and should be looked for, particularly in patients whose complaints suggest either hypothyroidism or psychoneurosis.

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SUMMARIO IN INTERLINGUA

Le Caso pro Hypometabolismo Euthyroide

Inter approximativemente 500 patientes scrutinate pro le controverso syndrome de hypometabolismo euthyroide, 32 esseva trovate (6,4%) qui satisfaceva le cinque criterios diagnostic pro le mentionate disordine proponite per le presente autor. Tal patientes monstrava normal valores de iodo ligate a proteina e un normal augmento del iodo ligate a proteina post administrationes de hormon thyroido-stimulante sed, nonobstante, valores pro le metabolismo basal e registrationes cinemometric del reflexo de Achilles in le ordine hypothyroido-hypometabolic. Ben que non responsive a placebos o a desiccate extractos thyroide, tal patientes respondeva favorabilemente—secundo criterios subjective e objective—al therapia con L-triiodothyronina. Le dosage de L-triiodothyronina variava inter 75 e 150 μg per die, con un valor medie de 112 μg per patiente. Un pejoration paradoxe del symptomat hypometabolic quando le patientes ricepeva insufficiente quantitates de L-triiodothyronina esseva notate. Iste phenomeno es discutite e etiam le necessitate de dishabituare tal patientes ab le uso de tranquilisatores ante le initiation del therapia a L-triiodothyronina. Ben que le ver etiologia e incidentia de hypometabolismo euthyroide remane indeterminate, le these es presentate que le existentia de iste syndrome es multo probabile e que su presentia deberea esser suspecte in patientes, super toto, con gravamines que suggere hypothyroidismo o psychoneurose.