H. J. Bonnell,[1] *M.D.*

Antemortem Chemical Hypothyroxinemia

REFERENCE: Bonnell, H. J., **"Antemortem Chemical Hypothyroxinemia,"** *Journal of Forensic Sciences*, JFSCA, Vol. 28, No. 1, Jan. 1983, pp. 242-248.

ABSTRACT: Based on reports of hypothyroidism in intensive care unit patients, a preliminary study was instituted in which 40 patients coming to autopsy, with no history of thyroid disease, were studied to include gross and microscopic study of the thyroid gland and the performance of thyroid function tests on all serum specimens submitted within seven days of death. Initial studies show that with the exception of sudden cardiac death, all of the autopsy patients showed evidence of chemical hypothyroxinemia within three days preceding death without any histologic abnormalities of the thyroid gland. Thyroid function tests were subsequently studied of decedents and survivor controls matched for age, sex, disease, and stage of disease if applicable. The findings were similar.

KEYWORDS: pathology and biology, hypothyroxinemia, chemical analysis

Incidental reports of chemical hypothyroidism in patients in intensive care units stimulated the performance of a preliminary study of thyroid function tests in seriously ill patients. The patients included in the initial study were 40 autopsied patients with no history of thyroid disease. The initial study was limited to patients undergoing autopsy so that microscopic analysis of thyroid tissue, which was not done in previous reports [*1,2*] could be performed.

Materials and Methods

Upon receipt of an autopsy permit, any serum routinely submitted by the attending physician within the previous seven days was retrieved. It was routine policy to refrigerate all serums submitted for chemical analysis and to retain these specimens for seven days. Following retrieval, all specimens were immediately frozen and subsequently thawed for analysis. To determine possible changes in test results due to prolonged refrigeration, the author donated 15 mL of serum, which was aliquoted into eight tubes, one being frozen immediately. The other specimens were refrigerated and one specimen was frozen each subsequent day. The variance between the specimen frozen immediately and that frozen eight days later was 0.2 μg/dL. Serum T4 and T3 uptake were measured by standard radioimmunoassay techniques and a free thyroxin index was calculated. All specimens were analyzed in duplicate and a variance of less than 10% was required for the test value to be acceptable. Thyroid stimulating hormone levels were not determined because of financial constraints: the study was not subsidized.

Received for publication 25 March 1982; revised manuscript received 1 June 1982; accepted for publication 2 June 1982.

[1]Office of the Medical Examiner, Seattle, WA.

Subjects

The basic pathology of the 40 patients included idiopathic pulmonary hypertension with cardiac failure, chronic obstructive pulmonary disease with bronchopneumonia, metastatic undifferentiated large cell carcinoma of the lung, bronchopneumonia with sepsis, pulmonary embolus, multiple myeloma, aplastic anemia, respiratory failure resulting from angioblastic lymphadenopathy, metastatic ductal carcinoma of the breast, perforated gastric ulcer with peritonitis, chronic myelogenous leukemia, cholangiocarcinoma, Hodgkin's lymphoma, three-week-old massive cerebrovascular accident, squamous cell carcinoma of the esophagus (two patients), ischemic bowel disease and sepsis (two patients), squamous cell carcinoma of the lung (two patients), pancreatic carcinoma (three patients), small cell carcinoma of the lung (three patients), bleeding esophageal varices (three patients), and arteriosclerotic heart disease (eleven patients).

Observations

The only patients in whom thyroid function tests remained normal were the patients with "sudden" deaths such as myocardial infarction with refractory arrhythmia or pulmonary embolus. In all other patients, whether described at autopsy as being cachectic or not, the following trend was noted. T4 levels dropped to below normal (less than 5.0 μg/dL) at least three days before death (Table 1). T3 uptake was higher than normal in some cases and lower than normal in others; there was no consistent pattern correlating with the underlying disease. All patients with an abnormally low calculated free thyroxin index also had an abnormally low T4 level. Sections of thyroid gland were routinely examined and no abnormalities were noted. None of the thyroid glands were enlarged or showed abnormalities upon gross examination (Table 1). This initial study suggested that in those patients whose primary disease process is not cardiovascular, there is an abnormally low T4 level at least three days antemortem.

As a result of these findings, a second study was begun to compare survivors with decedents, matching for age (within five years), sex, disease, and stage of the disease if applicable. Serum was saved and frozen, as described above, from all patients placed on the seriously ill roster of the hospital. The sera of another ten autopsied patients, who expired while on the seriously ill roster, were thawed and analyzed. These were then compared to the sera of 50 patients who were matched as above and who survived to be removed from the seriously ill roster (Table 2). In all cases of sudden cardiovascular events, the thyroid function tests were equivocal. But in nonsudden deaths, all decedents became hypothyroid at least three days before death. Three matched controls showed borderline hypothyroxinemia (between 4.7 and 5.0 μg/dL) on an individual specimen, but never on two consecutive days.

Discussion

Although these were all hospitalized patients, only two of the autopsied patients were on dopamine (patients 31 and 46) and neither was hypothyroxinemic. None of the patients were on anticonvulsants, penicillin, or heparin, drugs that have all been shown to alter thyroid function tests [*3–6*]. Dopamine, the precursor to norepinephrine, would be expected to activate adenyl cyclase in the thyroid gland, thus enhancing the accumulation of cyclic adenosine monophosphate [*7*], and to elevate T4 levels, but actually it lowers the T4 level [*2*]. A possible explanation of the low T4 level is that the rapidity of iodination and oxidative coupling of thyroid globulin is dependent on the level of glandular activity [*8*]. An exhausted gland may provide inadequate opportunity to fully iodinate the thyroglobulin, but this was not apparent in the normal histologic picture that was present.

A second possible explanation is at the other end of the hormonal life cycle, the receptor. T3 is more active than T4 but there are receptors for both in the chromatin of the nucleus,

TABLE 1—*Thyroid weights and T4 levels of autopsied patients.*

Sequence Number	Fresh Thyroid Weight, g	Serum T4 Levels, μg/dL, on Antemortem Day							Diagnosis
		7th	6th	5th	4th	3rd	2nd	1st	
1	21.4	7.6	...	4.1	...	2.1	0.3	0.3	esophageal varices
2	22.6	4.8	...	...	...	4.2	...	...	angioblastic lymphadenopathy
3	19.3	9.3	8.8	...	5.6	4.8	...	3.2	small cell carcinoma
4	19.1	4.3	3.9	...	3.1	...	2.2	1.7	chronic obstructive pulmonary disease
5	18.7	6.4	...	5.6	4.7	...	3.1	...	idiopathic pulmonary hypertension
6	20.2	3.3	...	...	1.7	...	...	...	cholangiocarcinoma
7	20.8	4.8	4.4	4.1	3.4	3.0	3.0	2.6	pancreatic carcinoma
8	18.1	...	8.2	8.6	8.9	8.4	8.0	...	arteriosclerotic heart disease
9	21.0	7.6	...	5.5	...	4.3	...	3.6	perforated ulcer
10	27.2	...	...	4.8	4.3	4.0	3.2	...	small cell carcinoma
11	19.5	8.4	8.1	7.4	6.2	4.9	3.3	2.6	ductal carcinoma
12	23.0	4.7	...	...	3.5	...	...	1.9	esophageal varices
13	19.5	8.5	8.3	8.6	8.4	...	...	9.2	arteriosclerotic heart disease
14	24.8	10.2	9.8	9.6	9.7	9.8	...	...	arteriosclerotic heart disease
15	21.3	3.1	...	...	1.9	...	...	1.2	multiple myeloma
16	22.6	3.8	...	3.6	...	3.0	...	2.6	lung, large cell carcinoma
17	19.4	7.3	...	7.2	7.1	7.4	7.6	...	arteriosclerotic heart disease
18	18.0	...	4.2	...	3.7	...	3.5	...	lung, squamous carcinoma
19	19.0	...	6.1	5.5	...	4.3	...	1.7	pancreatic carcinoma
20	21.5	...	...	3.2	...	...	...	2.6	esophageal carcinoma
21	23.3	3.6	...	3.3	...	3.0	2.9	...	chronic myelogenous leukemia
22	19.5	...	...	8.2	8.1	8.3	8.2	7.9	arteriosclerotic heart disease

23	20.1	8.2	...	6.8	...	4.0	...	...	bronchopneumonia and sepsis
24	26.5	1.9	...	...	1.3	...	1.0	...	aplastic anemia
25	22.1	9.6	9.4	9.2	8.6	7.8	8.2	8.6	pulmonary embolus
26	31.6	...	...	...	...	8.3	7.9	8.2	arteriosclerotic heart disease
27	20.5	6.4	...	6.6	...	4.8	...	4.2	esophageal varices
28	18.8	...	8.6	8.5	8.7	9.1	...	...	arteriosclerotic heart disease
29	23.0	7.0	5.6	5.7	5.2	4.9	4.3	4.1	ischemic bowel
30	22.5	5.2	...	...	4.8	...	...	3.9	small cell carcinoma
31	28.3	...	...	...	...	9.3	9.4	9.3	arteriosclerotic heart disease
32	26.4	4.2	...	3.6	...	3.4	...	3.3	hodgkin's lymphoma
33	30.5	5.8	...	...	4.9	...	4.2	...	lung, squamous carcinoma
34	18.7	...	...	7.6	7.4	7.7	7.6	7.5	arteriosclerotic heart disease
35	30.2	6.2	...	5.9	...	4.9	...	4.6	cerebrovascular accident
36	28.8	...	...	...	...	...	8.2	8.1	arteriosclerotic heart disease
37	22.8	7.3	7.0	6.2	5.5	4.7	4.4	4.3	esophageal carcinoma
38	18.5	...	...	10.1	9.8	10.0	10.2	9.9	arteriosclerotic heart disease
39	24.3	6.7	...	6.0	5.6	4.9	4.0	3.1	pancreatic carcinoma
40	22.5	4.6	4.5	4.5	4.3	3.9	4.0	3.8	ischemic bowel
41	26.7	...	...	8.4	8.2	8.0	8.1	7.9	arteriosclerotic heart disease
42	24.3	...	7.9	7.8	7.6	7.8	7.7	7.9	arteriosclerotic heart disease
43	20.1	6.2	...	5.8	...	4.9	...	4.2	lung, squamous carcinoma
44	21.8	...	5.1	4.7	4.3	3.9	3.0	2.8	lymphoma
45	23.9	2.0	...	...	1.2	...	...	1.1	small cell carcinoma
46	27.8	...	...	...	...	9.8	9.6	9.4	arteriosclerotic heart disease
47	29.6	6.2	5.8	5.1	4.6	...	4.0	...	esophageal carcinoma
48	22.7	4.7	...	4.3	...	3.2	...	2.9	pancreatic carcinoma
49	25.5	...	4.8	...	...	3.9	...	...	lung, adenocarcinoma
50	24.6	...	...	...	...	...	8.2	8.1	arteriosclerotic heart disease

TABLE 2—*Matched controls.*

Matched Control Sequence	Diagnosis	Age	Sex	Lowest T4, μg/dL
1	esophageal varices	47	M	6.2
2	angioblastic lymphadenopathy	38	M	7.2[a]
3	small cell carcinoma	42	M	5.7
4	chronic obstructive pulmonary disease	69	M	4.8
5	idiopathic pulmonary hypertension	29	M	8.2
6	cholangiocarcinoma	48	M	6.8
7	pancreatic carcinoma	51	M	5.8
8	arteriosclerotic heart disease	46	M	7.8
9	perforated ulcer	31	M	9.2
10	small cell carcinoma	47	M	6.1
11	ductal carcinoma	43	F	8.2
12	esophageal varices	58	M	6.8
13	arteriosclerotic heart disease	56	M	8.1
14	arteriosclerotic heart disease	42	M	9.7
15	multiple myeloma	53	F	8.2
16	lung, large cell carcinoma	48	M	7.1
17	arteriosclerotic heart disease	68	M	8.7
18	lung, squamous carcinoma	46	M	6.1
19	pancreatic carcinoma	42	M	7.3
20	esophageal carcinoma	61	M	6.8
21	chronic myelogenous leukemia	38	M	7.1
22	arteriosclerotic heart disease	53	M	9.6
23	bronchopneumonia and sepsis	48	M	7.7
24	aplastic anemia	49	M	5.0
25	pulmonary embolus	73	M	8.2
26	arteriosclerotic heart disease	38	M	9.3
27	esophageal varices	36	M	7.2
28	arteriosclerotic heart disease	57	M	9.9
29	ischemic bowel	74	M	6.7
30	small cell carcinoma	53	M	7.1
31	arteriosclerotic heart disease	68	M	8.3
32	hodgkin's lymphoma	28	M	4.7[b]
33	lung, squamous carcinoma	41	M	6.2
34	arteriosclerotic heart disease	46	M	10.6
35	cerebrovascular accident	79	M	7.4
36	arteriosclerotic heart disease	68	M	6.6
37	esophageal carcinoma	57	M	7.2
38	arteriosclerotic heart disease	41	M	9.4
39	pancreatic carcinoma	47	M	5.6
40	ischemic bowel	86	M	6.2
41	arteriosclerotic heart disease	56	M	9.8
42	arteriosclerotic heart disease	57	M	8.3
43	lung, squamous carcinoma	62	M	7.1
44	lymphoma	39	M	6.2
45	small cell carcinoma	47	M	5.9
46	arteriosclerotic heart disease	53	M	8.7
47	esophageal carcinoma	63	M	7.1
48	pancreatic carcinoma	53	M	6.8
49	lung, adenocarcinoma	49	M	8.1
50	arteriosclerotic heart disease	78	M	6.4

[a]Expired three months later.
[b]Expired five months later.

whether the hormone is present or not [9]. Hormonal uptake by cells proceeds readily although little is known about the exact mechanism. Thus, a low T4 level in the serum may reflect increased binding to receptors by the less active of the two hormones, accounting for varying and occasionally high T3 levels in the serum.

The most likely explanation is that T4 is deiodinated to T3 in extrathyroid tissue also, particularly liver and kidney, and that 80% of the daily production of T3 comes from this source, with the remaining 20% being produced by the thyroid [*10*]. Thus, the dying patient with a low T4 and high T3 may be manifesting increased liver and kidney activity in an attempt to generate the more active hormone. The dying patient with a low T4 and low T3 level may represent failure of the liver and kidney too. In either situation, the histologic picture of the thyroid gland is normal, suggesting that the changes are extrathyroid.

For the forensic pathologist, the vitreous sample is useless since postmortem values of T4 in the eye are not detectable as early as 2 h following death (personal experience) even though thyroglobulin-like material is found in normal human orbital muscle [*11*]. The postmortem values of T4 in the serum decrease with time, although the rate is highly variable, too unreliable for dating time of death [*12*]. In this study by Coe [*12*], an antemortem sample was analyzed but the collection time preceding death is not mentioned. However, the T4 values for those dying of arteriosclerotic heart disease are markedly higher than for those dying of other causes. One of the conclusions reached by Coe was that although postmortem values may be suggestive of hypothyroidism, no glandular abnormality existed. The findings presented here indicate that although antemortem values may be suggestive of hypothyroidism, again no glandular abnormality exists. Indeed, it is hypothyroxinemia and not hypothyroidism; as such, it is a manifestation of chronic disease and not the cause.

Conclusion

This study indicates that hypothyroxinemia is indeed common in debilitated, chronically ill patients such as alcoholics with bleeding varices and respiratory cripples. The forensic pathologist must exhibit great caution before considering hypothyroidism as a cause of death in the debilitated patient.

Acknowledgments

I would like to thank Dorothy Bjuhr, M.T., A.S.C.P., and Donna Roberts, M.T., A.S.C.P., for teaching me the methods of radioimmunoassay and trouble-shooting my problems.

References

[*1*] McLarty, D. G., Ratcliffe, W. A., McColls, K., Stone, D., Ratcliffe J. G., "Thyroid Hormone Levels and Prognosis in Patients with Serious Nonthyroid Illness," *Lancet*, No. 7928, 9 Aug. 1975, pp. 275-276.

[*2*] Slag, M. F., Morley, J. E., Elson, M. K., Crowson, T. W., Nuttall, F. Q., et al, "Hypothyroxinemia in Critically Ill Patients as a Predictor of High Mortality," *Journal of the American Medical Association*, Vol. 245, No. 1, Jan. 1981, pp. 43-45.

[*3*] Nicoloff, J. T., Fisher, D. A., and Appleman, M. D., "The Role of Glucocorticoids in the Regulation of Thyroid Function in Man." *Journal of Clinical Investigation*, Vol. 49, No. 10, Oct. 1970, pp. 1922-1929.

[*4*] Surks, M. I. and Oppenheimer, J. H., "Effects of Penicillin on Thyroxine Binding by Plasma Proteins," *Endocrinology*, Vol. 72, No. 4, April 1963, pp. 567-573.

[*5*] Liewendahl, K., Majuri, H., and Helenius, T., "Thyroid Function Tests in Patients with Long-Term Treatment with Various Anticonvulsant Drugs," *Clinical Endocrinology*, Vol. 8, No. 3, March 1978, pp. 185-191.

[*6*] Schatz, D. L., Sheppard, R. H., Steiner, G., Chandarlapaty, C. S., and deVeber, G. A., "Influ-

ence of Heparin on Serum Free Thyroxine," *Journal of Clinical Endocrinology and Metabolism*, Vol. 29, No. 8, Aug. 1969, pp. 1015-1022.

[7] Sato, A., Hashizume, K., Onaya, T., Miyakawa, M., Makiuchi, M., et al, "Effects of Biogenic Amines on the Formation of Adenosine 3′,5′-Monophosphate in Human Thyroid Slices," *Endocrinology Japan*, Vol. 23, No. 4, Aug. 1976, pp. 319-325.

[8] VanHerle, A. J., Vassart, G., and Dumont, J. E., "Control of Thyroglobulin Synthesis and Secretions," *New England Journal of Medicine*, Vol. 301, No. 5, Aug. 1979, pp. 239-248.

[9] Oppenheimer, J. H., Schwartz, H. L., Surks, M. I., Koerner, D., and Dillmann, W. H., "Nucleus Receptors and the Initiation of Thyroid Hormone Action," *Recent Progress in Hormone Research*, Vol. 32, 1976, pp. 529-557.

[10] Schimmel, M. and Utiger, R. D., "Thyroidal and Peripheral Production of Thyroid Hormones," *Annals of Internal Medicine*, Vol. 87, No. 6, Dec. 1977, pp. 760-768.

[11] Mullin, B. R., Levinson, R. E., Friedman, A., Henson, D. E., Winand, R. J., et al, "Delayed Hypersensitivity in Grave's Disease and Exophthalmos: Identification of Thyroglobulin in Normal Human Orbital Muscle," *Endocrinology*, Vol. 100, No. 2, Feb. 1977, pp. 351-366.

[12] Coe, J. I., "Postmortem Values of Thyroxine and Thyroid Stimulating Hormone," *Journal of Forensic Sciences*, Vol. 18, No. 1, Jan. 1973, pp. 20-24.

Address requests for reprints or additional information to
H. J. Bonnell, M.D.
Office of the Medical Examiner
325 Ninth Ave.
Seattle, WA 98104