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# Transient Stimulatory Effects on Pituitary-Thyroid Axis in Patients Treated with Interleukin-2

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It has been shown that various cytokine therapies may influence thyroid hormone parameters that may lead to serious side effects including nonthyroidal illness. Interleukin-2 is effective in increasing CD4-T cell numbers in human immunodeficiency virus (HIV)-infected patients and it is used in the treatment of various malignant tumours. However, the association of interleukin-2 (IL-2) therapy and thyroid function is not clearly established as serial systematic measurements of thyroid parameters have not been performed with interleukin-2 as the sole therapeutic agent. Therefore, it was the aim of this study to examine prospectively the impact of a 5-day interleukin-2 therapy on thyroid parameters in asymptomatic HIV-infected patients. Twenty male euthyroid patients (mean age, 42.6 ± 3.2 years; body weight, 73.4 ± 3.0 kg) received 9,000,000 IU/d interleukin-2. Thyroid function was evaluated by measurements of serum thyrotropin (TSH), triiodothyronine ($T_3$), thyroxine ($T_4$), free thyroxine ($FT_4$), reverse $T_3$ ($rT_3$), thyroglobulin (Tg), thyroxine-binding globulin (TBG), and anti-thyroid-peroxidase (TPO)-antibodies from day 1–4 and on days 7, 14, 20, 40, 60, 80, and 100. All results are given as mean ± SD. On day 4, we observed a significant increase that was still within normal range of $T_4$ and $T_3$ ($p < 0.05$). TSH increased from 1.33 ± 0.57 to 4.53 ± 1.39 mU/I ($p = 0.0001$) and $FT_4$ from 18.1 ± 4.2 to 48.9 ± 10.9 pmol/L ($p = 0.0001$) on day 4 with a gradual decrease thereafter. Normalization to baseline levels for TSH (1.45 ± 0.75 mU/L) and $FT_4$ (18.1 ± 3.0 pmol/L) was achieved only on day 14. The increase of $FT_4$ was more pronounced (well in the hyperthyroid range) than the increase in total $T_4$ in the presence of normal TBG and albumin concentrations whereas TBG was not affected. We did not observe changes in anti-TPO-antibody levels up to day 100. Our data clearly demonstrate that the administration of interleukin-2 has a stimulatory effect on the pituitary-thyroid axis. The increase of TSH suggests a central stimulation directed by the action of IL-2 as the major mechanism.

## Introduction

RECENTLY, SEVERAL STUDIES DEMONSTRATED a beneficial immunological effect of interleukin-2 (IL-2) therapy in human immunodeficiency virus (HIV) infection with a striking increase in the number of T lymphocytes (1–4). Furthermore, it is used in the treatment of malignant tumors, such as metastatic renal cell carcinoma and melanoma (5–7). IL-2 is the principal cytokine that induces T-cell activation and differentiation whereas most other cytokines have divergent functions on the immune system and are redundant in their action. IL-2 is unique in its action on T cells and can only marginally be substituted by other cytokines (8,9).

It has been reported that therapy with IL-2 in combination with other cytokines is associated with several serious side effects that may lead to the termination of therapy. Hypothyroidism and hyperthyroidism have been shown to occur after cytokine therapy, sometimes necessitating termination of the treatment (10–12). However, most studies found features of nonthyroidal illness after the administration of cytokines, such as IL-1 or 6 (10,13,14). In contrast to IL-2, these cytokines have divergent actions on many cells of the immune system, particularly activating nonspecific inflammatory responses.

The association of IL-2 therapy and thyroid function, however, has not been clearly established because serial systematic measurements of thyroid parameters have not been performed using IL-2 as the sole therapeutic agent (15–20). Asymptomatic patients with HIV disease display normal thyroid hormone parameters with only modest increases in TBG concentrations that are well within the normal range (21).

Therefore, it was the good of this study to examine

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TABLE 1.

| Day | TSH (mU/L) (0.3–4.0) | $T_3$ (nmol/L) (0.9–3.1) | $T_4$ (nmol/L) (50–158) | $FT_4$ (pmol/L) (10–25) | $rT_3$ (ng/mL) (0.09–0.35) | Tg (ng/mL) (10–40) | TBG (mg/L) (10–35) |
|---|---|---|---|---|---|---|---|
| 0 | 1.33 ± 0.57 | 2.09 ± 0.43 | 85 ± 20 | 18.1 ± 4.2 | 0.21 ± 0.08 | 36.0 ± 26.1 | 21.6 ± 4.1 |
| 4 | 4.53 ± 1.39 | 2.54 ± 0.46 | 120 ± 23 | 48.9 ± 10.9 | 0.26 ± 0.08 | 49.0 ± 30.4 | 21.2 ± 3.9 |
| | $p = 0.0001$ | $p = 0.0338$ | $p = 0.016$ | $p = 0.001$ | $p = 0.1017$ | $p = 0.3347$ | $p = 0.7988$ |
| 7 | 3.39 ± 1.73 | 2.34 ± 0.43 | 101 ± 23 | 31.0 ± 10.2 | 0.25 ± 0.07 | 54.7 ± 33.1 | 20.9 ± 4.1 |
| | $p = 0.0001$ | $p = 0.1981$ | $p = 0.0929$ | $p = 0.0001$ | $p = 0.1927$ | $p = 0.1399$ | $p = 0.6595$ |
| 14 | 1.45 ± 0.75 | 2.09 ± 0.34 | 89 ± 24 | 18.1 ± 3.0 | 0.24 ± 0.07 | 50.4 ± 34.3 | 20.8 ± 3.5 |
| 20 | 1.42 ± 0.68 | 2.15 ± 0.42 | 86 ± 20 | 19.1 ± 5.0 | 0.22 ± 0.08 | 45.2 ± 24.4 | 21.7 ± 3.8 |
| | $p = 0.727$ | $p = 0.7461$ | $p = 0.8309$ | $p = 0.5062$ | $p = 0.6228$ | $p = 0.3740$ | $p = 0.9570$ |

TSH, thyrotropin; $T_3$, triiodothyronine; $T_4$, thyroxine; $FT_4$, free thyroxine; $rT_3$, reverse triiodothyronine; Tg, thyroglobulin; TBG,

prospectively the impact of a 5-day regimen of IL-2 therapy on thyroid parameters in asymptomatic HIV-infected patients.

## Patients and Methods

Patients who were 18 years and older, with HIV-infection were treated with IL-2 as previously reported (22). The 20 male patients (mean age, 42.6 ± 3.2 years; body weight, 73.4 ± 3.0 kg; time from first diagnosis of HIV infection: 35 ± 8 months) provided written informed consent. Patients had to be in a stable clinical situation without any signs of acute or chronic opportunistic infections. All patients were euthyroid as assessed by normal thyrotropin (TSH), triiodothyronine ($T_3$), free thyroxine ($FT_4$), and negative thyroid peroxidase (TPO) and TSH-receptor antibodies, and none of the patients received thyroid hormones. Patients received 9 Mio. IU/day IL-2 (Aldesleukin, Proleukin, Chiron, Ratingen, Germany) either intravenously or subcutaneously. We had previously shown that both protocols were similar regarding their immunological consequences as far as numbers of CD4 and CD8 positive lymphocytes and HIV viral load were concerned (22). Treatment was performed for up to 5 days or until adverse events or severe constitutional symptoms (fever higher than 39.5°C, malaise, headache) precluded further therapy. Treatment with acetaminophen, novaminsul-

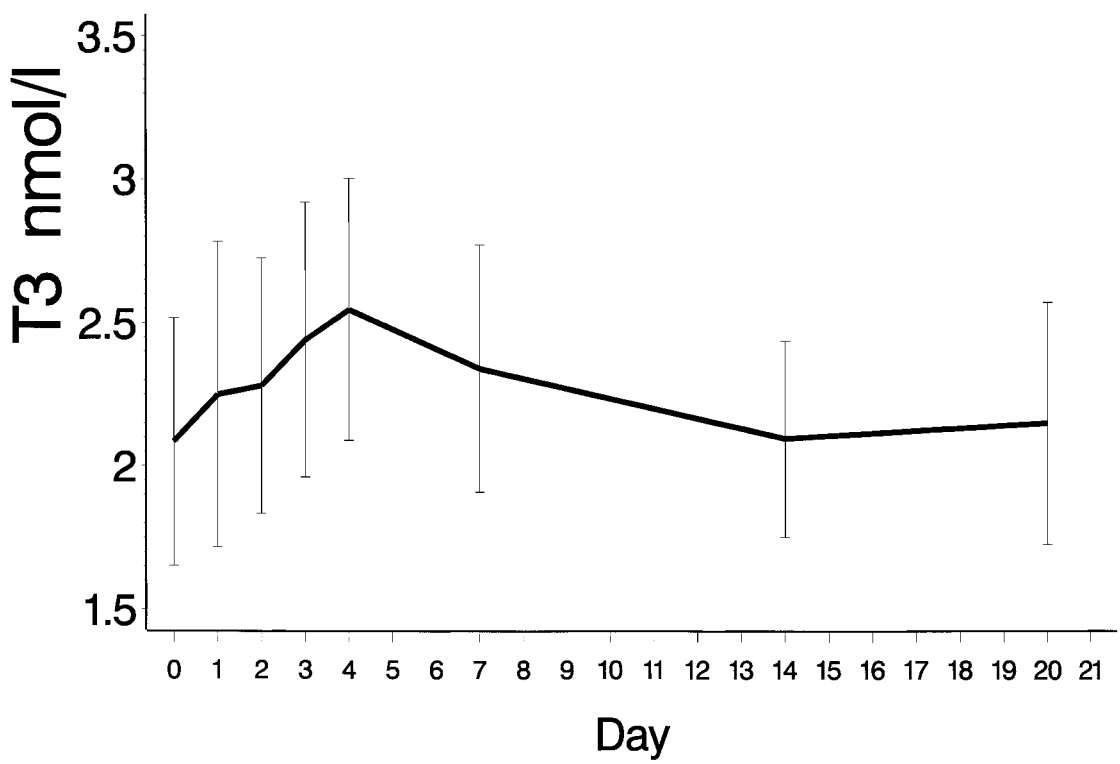


**FIG. 1.** Triiodothyronine ($T_3$) serum levels in the course of the interleukin-2 (IL-2) treatment protocol. There is a significant increase of $T_3$ levels after IL-2 treatment with a peak level on day 4. All values are given as mean ± SD.

fone, and antiemetic agents was permitted to treat such constitutional symptoms. A total of 3 patients received metoclopramide in an oral dose of 1–2 × 10 mg on day 2 (1 patient), on day 3 (3 patients), and on day 4 (1 patient).

Furthermore all patients were treated with a combination of HIV antiviral drugs (usually two reverse-transcriptase inhibitors and one protease-inhibitor). The antiviral treatment was started at least 6 weeks prior to the start of the study and was maintained throughout the whole period of the study.

Immunological parameters (hematocrit, differential blood count, number of $CD4^+$ and $CD8^+$ lymphocytes, HIV-viral load) were measured in regular intervals. Thyroid function was evaluated by measurements of serum TSH (normal range, 0.3–4.0 mU/L), $T_3$ (normal ranges, 0.9–3.1 nmol/L), $T_4$ (normal range, 50–158 nmol/L), $FT_4$ (normal range, 10–25 pmol/L), $rT_3$ (normal range, 0.09–0.35 ng/mL), Tg (normal range, 10–40 ng/mL), TBG (10–35 mg/L) and anti-TPO-antibodies from day 1–4 and on days 7, 14, 20, 40, 60, 80, and 100. All samples were taken in the morning between 8–9 A.M. In order to avoid interassay variability all samples for one patient were measured in one assay. Total $T_3$, total $T_4$, $FT_4$, and TSH were measured by immunoluminescence-assay (ACS Ciba Corning), anti-TPO antibodies by enzyme-immunoassay (Anti-TPO, Fa, Biermann, Bad Nauheim, Germany), reverse $T_3$ by radioimmunoassay (Biochem. Immunosystems Cie, Freiburg, Germany). TBG was measured by radioimmunoassay (Brahms, Germany, Berlin), and Tg by luminescence-assay (Brahms).

All results are given as mean ± SD. Statistical analysis was performed using the SAS program. General linear models procedure for repeated measures was performed to compare results for different thyroid hormone parameters during the course of time. The study was not sponsored by a company and was approved by the local ethical committee.

## Results

IL-2 therapy was maintained for a mean period of 4.5 ± 0.1 days. Only 7 patients completed the full cycle of 5 days of treatment but all patients received at least 4 days of treatment. Therapy was stopped in these remaining 13 patients because of side effects such as fever, hypotension, myalgias, exanthema, nausea, fatigue, and malaise.

IL-2 administration was associated with significant increases in the number of $CD4^+$ lymphocytes (baseline: 298 ± 62 cells per microliter to a maximum on day 7: 712 ± 171 cells per microliter $p < 0.001$). This increment in the number of $CD4^+$ lymphocytes persisted for more than 100 days (day 100: 410 ± 46 cells per microliter) (22). Hematocrit decreased more than 3 g/dL in 7 of 20 patients.

On day 4, we observed a significant increase within the normal range of $T_4$ and $T_3$ (Table 1, Figs. 1 and 2). $rT_3$ was within the normal limits at the beginning of the study with no significant increase during the further observation period. TSH increased from 1.33 ± 0.57 to 4.53 ± 1.39 mU/L ($p = 0.0001$) and $FT_4$ from 18.1 ± 4.2 to 48.9 ± 10.9 pmol/L ($p = 0.0001$) on day 4 with a gradual decrease thereafter (Figs. 3 and 4). Normalization to baseline levels for TSH (1.45 ± 0.75 mU/L) and $FT_4$ (18.1 ± 3.0 pmol/L) was achieved only on day 14. All patients presented a uniform pattern of their thyroid hormone parameters. Tg levels were in the high-normal range on day 0. The small increase of Tg from day 0 to day

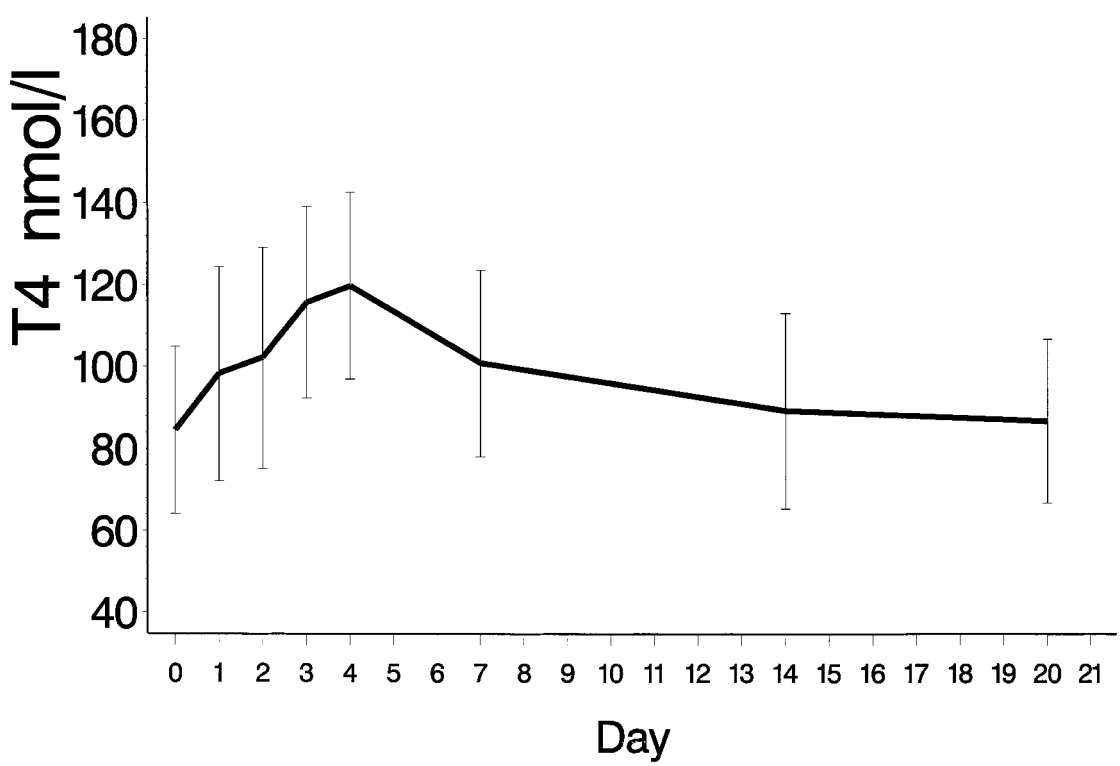


**FIG. 2.** Thyroxine ($T_4$) serum levels in the course of the interleukin-2 (IL-2) treatment protocol. There is a significant increase of $T_4$ levels after IL-2 treatment with a peak level on day 4. All values are given as mean ± SD.

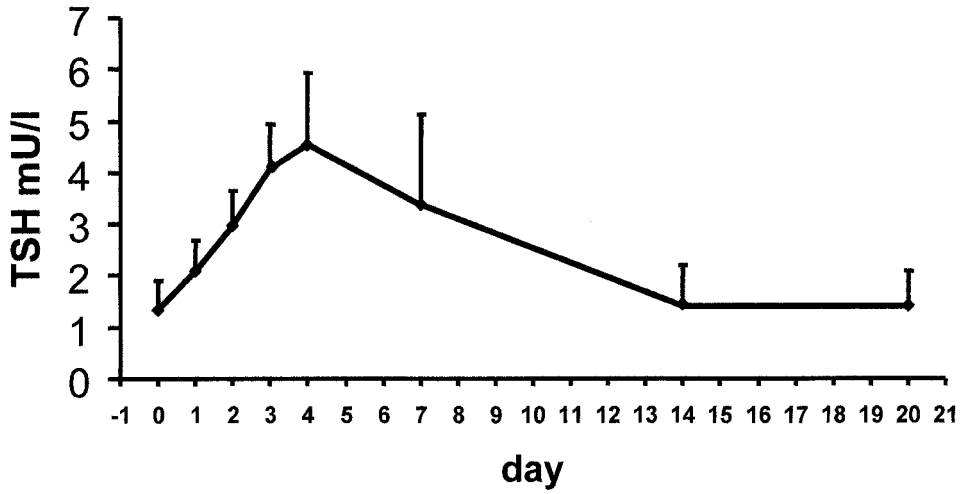


**FIG. 3.** Thyrotropin (TSH) serum levels in the course of the interleukin-2 (IL-2) treatment protocol. There is a significant increase of TSH levels after IL-2 treatment with a peak level on day 4. All values are given as mean ± SD.

7 was not statistically significant ($p = 0.1399$). TBG was not affected by IL-2 administration. We did not observe changes in TPO-antibody levels up to day 100.

Also no further changes were seen beyond day 20 in any of the parameters measured (data not shown). Results were not different in the three patients receiving metoclopramide (data not shown).

### *Discussion*

These data clearly demonstrate that the administration of IL-2 has a stimulatory effect on the pituitary-thyroid axis within days. We found a significant increase of TSH to levels slightly above the normal range and the peripheral thyroid hormone parameters $T_4$ and $T_3$ to the upper normal range with a gradual decrease after IL-2 treatment was stopped.

These data are in contrast to findings in other studies evaluating thyroid function after cytokine administration.

So far studies were carried out to evaluate the long-term effects of continuous IL-2 treatment either alone or in combination with interferon-$\alpha$ (IFN-$\alpha$) or tumor necrosis factor-$\alpha$ (TNF-$\alpha$). Krouse et al. (16) reported hypothyroidism in 35% and hyperthyroidism in 7% of patients treated with IL-2 alone for metastatic renal cell carcinoma or melanoma. However, the IL-2 preparations available at the time of this study were clearly different from the recombinant IL-2 used for our study. Thus, the dosage/effect ratio may be different in the study by Krouse et al. (16). This study did not have a defined time frame for the testing of the thyroidal hormone levels and the patient population was more heterogenous (16). Further

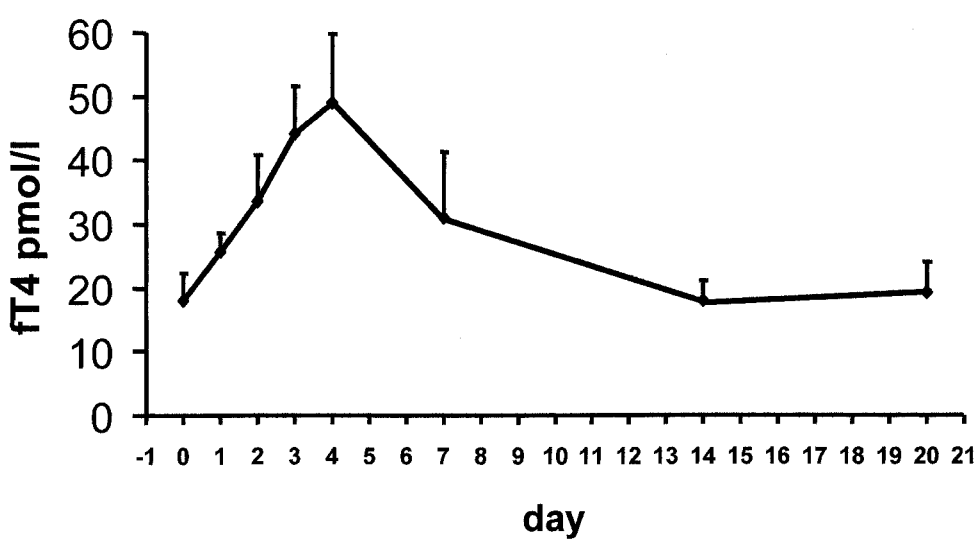


**FIG. 4.** Free thyroxine ($FT_4$) serum levels in the course of the interleukin-2 (IL-2) treatment protocol. There is a significant increase of $FT_4$ concentrations following IL-2 treatment with a peak on day 4. All values are given as mean ± SD.

support for this comes from the fact that our patients showed a very uniform response in their thyroidal response whereas this was not the case in the study by Krouse et al. (16).

Vassilopoulou-Sellin et al. (20) observed hyperthyroidism within the first 4 weeks of IL-2 administration in combination with either IFN-$\alpha$ or TNF-$\alpha$. The technetium uptake by the thyroid gland was negative during the hyperthyroid period and during a period of hypothyroidism in the following weeks suggesting silent thyroiditis in the absence of detectable anti-thyroid antibodies (20). Monig et al. (17) reported similar results in patients receiving a combined IL-2 and IFN-$\alpha$ therapy for metastatic melanoma. Here the authors observed frank hyperthyroidism in 3 of 17 patients with also a reduction in TSH levels in the remaining 14 patients. Again, thyroid hormone antibodies were unaffected (17). However, permanent hypothyroidism was reported by Sauter et al. (18) after a period of hyperthyroidism with a concomitant increase of antimicrosomal antibodies during combined IL-2/IFN-$\alpha$ therapy suggesting precipitating autoimmune thyroiditis (18,23). Scalzo et al. (19) observed hypothyroidism in 4 of 20 patients with renal cancer or malignant melanoma receiving combined IL-2/IFN-$\alpha$ therapy with preexisting antithyroid antibodies in 1 of these patients. However, the studies using combination cytokine therapy failed to clearly identify the effects on thyroidal hormone responses of the different cytokines used.

In contrast to these studies, we found no evidence of primary hypothyroidism or hyperthyroidism during the short-term IL-2 administration. Our patients were in good clinical condition prior to treatment and thyroid hormone parameters were well within normal limits. However, all of the patients experienced a period of severe side effects with fever, malaise, and fatigue. Therefore, we expected some form of nonthyroidal illness (i.e., low-$T_3$ and elevated $rT_3$ in the presence of low-normal TSH levels) during the course of IL-2 treatment (24–27). However, we found an increase of $T_3$ and $T_4$ with stable $rT_3$ levels. The concomitant rise of TSH suggests a central stimulation directed by the action of IL-2. This hypothesis is supported by *in vitro* findings from Karanth et al. (28) showing a direct stimulation of IL-2 on pituitary TSH release. Although one might expect a preferential release of $T_3$ in the presence of a rise in TSH, we observed a parallel increase of $T_3$, $T_4$, and $FT_4$. However, a relevant $T_3$ release might occur during the first 24 hours, but samples were not collected within this early time period. The increase of $FT_4$ was more pronounced (well in the hyperthyroid range) than the increase in total $T_4$ in the presence of normal TBG and albumin concentrations. This may suggest that IL-2 has an additional effect on the binding-affinity of $T_4$ to its binding-proteins. Tg was in the upper normal range prior to treatment with just a small increase on day 7. The kinetics of $T_4$ and Tg concentrations reflect the normal pattern after TSH stimulation, again emphasizing direct central stimulation of the pituitary-thyroid axis by the IL-2 treatment as the basic mechanism (29).

Furthermore, we were interested whether the thyroidal effects observed in our studies could be due to secondary immunological effects induced by IL-2. In contrast to our findings, however, Boelen et al. (30) have observed the laboratory features of nonthyroidal illness after systemic IL-6 therapy, a cytokine that is generally associated with symptoms of fever, malaise, and fatigue (30). An inverse correlation between IL-6 and $T_3$ concentrations was found in this study. Similar findings were observed in a different study using long-term IL-6 therapy (13). In an animal model IL-1, a cytokine also known for its pyrogenic properties, exerts suppressive effects on $T_3$, $T_4$, and TSH concentrations (11). Thus, it is very unlikely that the thyroidal effects observed in our study were mediated by the secondary induction of other cytokines, such as IL-1 and IL-6.

In conclusion, we were able to demonstrate that IL-2 has a stimulatory effect on the pituitary-thyroid axis within a few days. Our data suggest a direct stimulatory effect of IL-2 on pituitary TSH release and an additional effect on the binding-affinity of $T_4$ to its binding-proteins.

## References


1. Chun TW, Engel D, Mizell SB, Hallahan CW, Fischette M, Davey RT, Dybul M, Kovacs JA, Metcalf JA, Mican JM, Berrey MM, Corey L, Lane HC, Fauci AS 1999 Effect of interleukin-2 on the pool of latently infected, resting CD4 T cells in HIV-1 infected patients receiving highly active antiretroviral therapy. Nat Med **5:**651–655.
2. Hengge UR, Goos M, Esser S, Exner V, Dotterer H, Wiehler H, Borchard C, Muller K, Beckmann A, Eppner MT, Berger A, Fiedler M 1998 Randomised controlled phase II trial of subcutaneous interleukin-2 in combination with highly active antiretroviral therapy (HAART) in HIV patients. AIDS **12:**F225–234.
3. Kovacs JA, Baseler M, Dewar RJ, Vogel S, Davey RT, Falloon J, Polis MA, Walker RE, Stevens R, Salzmann NP 1995 Increases in CD4-T-lymphocytes with intermittent courses of interleukin-2 in patients with human immunodeficiency virus infection. N Engl J Med **332:**567–575.
4. Levy Y, Capitant C, Houhou S, Carriere I, Viard JP, Goujard C, Gastaut Ja, Oksenhendler E, Boumsell L, Gomard E, Rabian C, Weiss L, Guillet JG, Delfraissy JF, Aboulker JP, Seligmann M 1999 Comparison of subcutaneous and intravenous interleukin-2 in asymptomatic HIV-1 infection: A randomised controlled trial. ANRS 048 study group. Lancet **353:**1923–1929.
5. Weiss GR, Margolin KA, Aronson FR, Sznol M, Atkins MB, Dutcher JP, Gaynor ER, Boldt DH, Doroshow JH, Bar MH 1992 A randomized phase II trial of continuous infusion interleukin-2 or bolus injection interleukin-2 plus lymphokine-activated killer cells for advanced renal cell carcinoma. J Clin Oncol **10:**753–759.
6. West WH, Tauer KW, Yanelli JR, Marshall GD, Orr D, Thurman GB, Oldham RK 1987 Constant–infusion recombinant interleukin-2 in adoptive immunotherapy of advanced cancer. N Engl J Med **316:**898–905.
7. West WH 1989 Continuous infusion recombinant interleukin-2 (rIL-2) in adoptive cellular therapy of renal carcinoma and other malignancies. Cancer Treat Rev **16**(Suppl A):83–89.
8. Pantaleo G 1997 How immune-based interventions can change HIV therapy. Nat Med **3:**483–486.
9. Smith KA 1998 Interleukin-2: Inception, impact, and implications. Science **240:**1169–1176.
10. Bartalena L, Brogioni S, Grasso L, Veluzzi F, Martino E 1994 Relationship of the increased serum interleukin-6 concentration to changes of thyroid function in nonthyroidal illness. J Endocrinol Invest **17:**269–274.
11. Hermus ARMM, Sweep CGJ, van der Meer MJM, Ross HA, Smals AG, Benraad TJ, Kloppenburg PW 1992 Continuous

infusion of interleukin-1$\beta$ induces a nonthyroidal illness syndrome in the rat. Endocrinology **131:**2139–2146.
12. Kirchner H, de Riese W, Allhoff E, Atzpodien J 1991 Immunotherapy of advanced renal cell cancer using subcutaneous recombinant interleukin-2 and interferon-alpha. World J Urol **9:**219–222.
13. Stouthard JML, van der Poll T, Endert E 1994 Effects of acute and chronic interleukin-6 administration on thyroid hormone metabolism in humans. J Clin Endocrinol Metab **79:**1342–1346.
14. Boelen A, Platvoet-ter Schiphorst MC, Wiersinga WM 1997 Immunoneutralization of interleukin-1, tumor necrosis factor, interleukin-6 or interferon does not prevent the LPS-induced sick euthyroid syndrome in mice. J Endocrinol **153:**115–122.
15. Jacobs EL, Clare-Salzler MJ, Chopra IJ, Figlin RA 1991 Thyroid function abnormalities associated with the chronic outpatient administration of recombinant interleukin-2 and recombinant interferon-$\alpha$. J Immunother **10:**448–455.
16. Krouse RS, Royal RE, Heywood G, Weintraub BD, White DE, Steinberg SM, Rosenberg SA, Schwartzentruber DJ 1995 Thyroid dysfunction in 281 patients with metastatic melanoma or renal carcinoma treated with interleukin-2 alone. J Immunother Emphasis Tumor Immunol **18:**272–278.
17. Monig H, Hauschild A, Lange S, Folsch UR 1994 Suppressed thyroid-stimulating hormone secretion in patients treated with interleukin-2 and interferon-alpha 2b for metastatic melanoma. Clin Invest **72:**975–978.
18. Sauter NP, Atkins MB, Mier JW, Lechan RM 1992 Transient thyrotoxicosis and persistent hypothyroidism due to acute auto-thyroiditis after interleukin-2 and interferon-alpha therapy for metastatic carcinoma: A case report. Am J Med **92:**441–444.
19. Scalzo S, Gengaro A, Boccoli G, Masciulli R, Gianella G, Salvo G, Marolla P, Carlini P, Massimini G, Holdener EE 1990 Primary hypothyroidism associated with interleukin-2 and interferon-alpha therapy of melanoma and renal carcinoma.
20. Vassilopoulou-Sellin R, Sella A, Dexeus FH, Theriault RL, Pololoff DA 1992 Acute thyroid dysfunction (thyroiditis) after therapy with interleukin-2. Horm Metab Res **24:**434–438.
21. LoPresti JS, Fried JC, Spencer CA, Nicoloff JT 1989 Unique alterations of thyroid hormone indices in the acquired immunodeficiency syndrome (AIDS). Ann Intern Med **110:**970–975.
22. Witzke O, Winterhagen T, Reinhardt W, Heemann U, Grosse-Wilde H, Kreuzfelder E, Roggendorf M, Philipp Th 1998 Comparison between subcutaneous and intravenous interleukin-2 treatment in HIV disease. J Intern Med **244:**235–240.
23. Pichert G, Jost LM, Zobeli L, Odermatt B, Pedia G, Stahel RA 1990 Thyroiditis after treatment with interleukin-2 and interferon-alpha-2a. Br J Cancer **62:**100–104.
24. Boelen A, Platvoet-ter Schiphorst MC, Wiersinga WM 1995 Soluble cytokine receptors and the low 3,5,3′-triiodothyronine syndrome in patients with nonthyroidal disease. J Clin Endocrinol Metab **80:**971–976.
25. Boelen A, Platvoet-ter Schiphorst MC, Wiersinga WM 1996 Relationship between serum 3,5,3′-triiodothyronine and serum interleukin-8 interleukin-10 or interferon-$\gamma$ in patients with nonthyroidal illness. J Endocrinol Invest **19:**480–483.
26. Chopra IJ, Sakane S, Chua Teco GN 1991 A study of the serum concentration of tumor necrosis factor–alpha in thyroidal and nonthyroidal illnesses. J Clin Endocrinol Metab **72:**1113–1116.
27. Van der Poll T, Romijn JA, Wiersinga WM, Sauerwein HP 1990 Tumor necrosis factor: A putative mediator of the sick euthyroid syndrome in man. J Clin Endocrinol Metab **71:**1567–1572.
28. Karanth S, McCann SM 1997 Anterior pituitary hormone control by interleukin-2. Proc Natl Acad Sci USA **88:**2961–2965.
29. Uller RP, van Herle AJ, Chopra IJ 1973 Comparison of alterations in circulating thyroglobulin triiodothyronine and thyroxine in response to exogenous (bovine) and endogenous (human) thyrotropin. J Clin Endocrinol Metab **37:**741–748.
30. Boelen A, Platvoet-ter Schiphorst MC, Wiersinga WM 1993 Association between serum interleukin-6 and serum 3,5,3′-triiodothyronine in nonthyroidal illness. J Clin Endocrinol Metab **77:**1695–1699.

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