present in the skin.⁶ The same phenomenon has been noted in borderline lepromatous patients, particularly after one or two years of treatment. This is presumably because Schwann cells, in which most of the bacilli are contained, are relatively long-lived. In this situation probably the surface antigens of the bacillus are rarely exposed; soluble cytoplasmic antigens are more likely to be exposed but they are probably released slowly, so that few lymphocytes are sensitised. In reactions there appears to be a sudden increase in the release of these cytoplasmic antigens, though the trigger mechanism is unknown. Subsequent destruction of the Schwann cells may then lead to increased exposure of bacillary surface antigens, and it was noted that in five of the eight patients with nerve reactions there was a rise in LT responses when whole *M leprae* was used as antigen in the weeks after the reaction began.

In skin reactions the LT results indicate that there may be an increased exposure of bacillary surface antigens. In borderline tuberculoid leprosy few bacilli are present in the skin and they are predominantly found in the dermal nerves. It appears that the lymphocytes and macrophages in the skin suddenly recognise the bacilli in the dermal nerves, with destruction of the Schwann cells and consequent exposure of surface antigens. This possibility is borne out by the observation that in eight out of 10 of our patients with skin or mixed reactions who had skin biopsies during reaction large nerves were present containing degenerate bacilli within granuloma.

In mixed reactions hypersensitivity reaction in nerves often occurs weeks after the reaction in skin. This may be because some cytoplasmic antigens are released during the "skin phase" with increased lymphocyte sensitisation to these antigens, leading to increased recognition of such antigens elsewhere—particularly those in nerves.

Although the trigger mechanism for these reactions remains unknown, it has been suggested that coincidental exposure to other mycobacteria¹ may be a cause. There is no good evidence for this, however, and in those of our patients on whom LT tests were performed using BCG and *M duvalii* as antigens during reactions there was no consistent concomitant rise in responses.

Reversal reactions are of great importance as they may lead to nerve destruction almost overnight. Unfortunately this usually occurs when the patient is receiving antileprosy treatment, the more so if he has been diagnosed at an early stage of the disease, before nerve damage has occurred. It is important to elucidate the precipitating factors that cause these reactions, and when this is achieved it may be possible to prevent them.

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Thyroid hormones in the elderly sick: "T₄ euthyroidism"

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Summary

Thyroid function and serum levels of triiodothyronine (T₃) and thyroxine (T₄) were investigated in 79 euthyroid geriatric patients. Of the 59 inpatients and 20 outpatients 35 (59%) and 2, respectively, had low T₃ levels. In contrast, 7 (12%) and 6 (30%), respectively, had raised T₄ levels. Two further patients were excluded from the study because of raised levels of thyroid-stimulating hormone. Thyroxine-binding globulin was greatly increased in both groups of patients, but low serum albumin levels were present in 31 (39%). Despite these changes free T₃ and T₄ indices closely followed total T₃ and T₄

levels. The difference between the two groups of patients did not correlate with body weight, diagnostic categories, age, drug treatment, or duration of stay in hospital.

Introduction

Low blood levels of triiodothyronine (T₃) are common in debilitating diseases.¹ In view of the reported prevalence of thyroid disease in the elderly²⁻⁴ (which is disputed by some workers⁵⁻⁶) we investigated thyroid function and serum levels of T₃ and thyroxine (T₄) in patients in our geriatric hospital.

Patients and methods

Sera were obtained from 64 inpatients (mean age 79.6 years, range 69-95 years) and 24 outpatients (mean age 81.8 years, range 65-93 years). About a third of the inpatients were chronically disabled or ill to a degree preventing their return home, though most were eventually discharged, and a third were convalescent or being rehabilitated after acute episodes. These patients were studied between two and 30 weeks after admission. The remaining inpatients were studied within one week of admission, having suffered an acute episode or gradual general deterioration sufficient to need admission. There was no difference in our findings between the three groups. All had multiple disorders, usually referable to the cardiovascular or nervous system. Nine (14%) died within six weeks of our studies.

The outpatients were attending for follow-up after discharge or for maintenance of contact with social or rehabilitation services. Their general medical condition differed from that of the longer-stay

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inpatients, mainly in mobility rather than diagnosis. Owing to the difficulty of assembling a truly "healthy" geriatric control group, and because most hospitals use normal ranges unrelated to the elderly, we compared our patients with healthy adults aged 18-50 years.

Total T3 and T4 concentrations were measured by radioimmunoassay⁷ using antisera previously described.⁸ Values outside the normal range were checked at two dilutions. Free T3 and T4 indices (FT3I and FT4I) were calculated as $(100 \times \text{serum T3})/\text{Thyopac-3}$ and as $(10 \times \text{serum T4})/\text{Thyopac-3}$ respectively. Serum thyroid-stimulating hormone (TSH) was measured by standard double-antibody radioimmunoassay, MRC standard 68/38 being used. Thyroxine-binding globulin (TBG) was measured by radioimmunoassay.⁹ Albumin was measured by a standard autoanalyser method. Neither total T3, total T4, FT3I, FT4I, nor TSH were normally distributed, and the distribution was not made normal by using logarithms. We therefore give means and ranges, P values being derived using Wilcoxon's rank sum test.

Results

Thyroid disease—Two clinically euthyroid patients (2.3%) out of the total of 88 tested were excluded because of raised basal TSH levels, showing an exaggerated response to an injection of thyrotrophin-releasing hormone (TRH)¹⁰ and a low FT4I; in neither patient were thyroid antibodies detected, but we consider both to have been mildly hypothyroid. No patient was thought to be thyrotoxic. Two had raised FT3I and basal TSH levels below the detection limit of the assay, but both showed a rise in TSH after TRH. Thyroid haemagglutination antibodies were detected in four out of 39 patients tested (10.3%), which was in line with other reports¹¹; none was hypothyroid clinically or biochemically and all had normal TSH levels.

Other clinical aspects—Five patients taking drugs known to influence protein binding of T3 or T4 or to convert T4 to T3—four on phenytoin and one on oestrogens—were excluded, leaving 59 inpatients and 20 outpatients in the study. The usage of other drugs, age distribution, and, surprisingly, body weight were similar in the two groups and did not correlate with serum T3 (table I). In the inpatients a trend towards lower T3 levels in long-stay patients (less than two weeks: mean T3 1.44 nmol/l (0.94 ng/ml); over two weeks: mean T3 1.32 nmol/l (0.86 ng/ml)) was not significant statistically, even when further

TABLE I—Correlation between low T3 levels and clinical factors. Distribution between subgroups of T3 levels below 1.31 nmol/l (0.98 ng/ml). (Identical results were obtained for T3 levels below 1.08 nmol/l (0.70 ng/ml))

Factor tested	P for correlation*	
	Inpatients	All patients
Body weight (in kg: <40, 41-50, 51-60, 61-70, ≥71, or combinations)	>0.05	>0.05
Major diagnostic subgroup (cerebrovascular, cardiac, arthritis, anaemia, chest infection, diabetes, peripheral vascular, fractures, renal failure, or combinations)	>0.05	See table II
Duration of admission (in weeks: <1, 1-2, 2-6, ≥6, or combinations)	>0.05	—
Drugs (diuretics, digoxin, antibiotics, sedatives, other, none, or combinations) ..	>0.05	>0.05
Age (5- or 10-year cells, 65-85 or more, or combinations)	>0.05	>0.05

*P values for χ^2 derived from two-row contingency tables (Brandt and Snedecor's formula). By Fisher's exact test: P>0.05 for difference between any individual cell and mean of all cells.

TABLE III—Mean values in euthyroid geriatric patients and normal people. Ranges and number of people studied are given in parentheses

	Normal people	Geriatric outpatients	Geriatric inpatients
Serum T3 (nmol/l)	2.04 (1.51-2.76) (n = 35)	2.12 (1.23-3.07) (n = 20)	1.40*† (0.61-2.76) (n = 59)
Serum T4 (nmol/l)	99.4 (59.2-140.3) (n = 35)	126.1* (73.4-180.2) (n = 20)	114.7* (54.1-214.9) (n = 59)
Thyopac-3 index	102 (94-122) (n = 22)	106.6† (93.0-123.0) (n = 20)	98.7§ (77.0-120.0) (n = 59)
FT3I	1.25 (0.93-1.62) (n = 17)	1.29 (0.82-2.14) (n = 20)	0.91*† (0.41-1.64) (n = 59)
FT4I	7.16 (5.3-8.8) (n = 19)	9.20* (5.6-14.1) (n = 20)	9.04* (4.3-15.2) (n = 59)
TBG mg/l	9.46 (7.9-10.6) (n = 17)	13.6* (10.7-19.7) (n = 20)	12.3*§ (8.4-16.8) (n = 58)
Albumin g/l	39.0 (30.0-50.0) (n = 50)	33.9* (28.0-46.0) (n = 20)	32.1* (24.0-45.0) (n = 58)
TSH mU/l	2.14 (<0.50-4.20) (n = 35)	1.83* (<0.50-4.60) (n = 20)	1.85* (<0.50-4.30) (n = 57)

*†P for difference from normal subjects: *P<0.005; †P<0.05.

‡§P for difference between inpatients and outpatients: ‡P<0.005; §P<0.05.

Other differences not significant (Wilcoxon's rank sum test).

Conversion: SI to traditional units—T3: 1 nmol/l $\approx$ 0.65 ng/ml. T4: 1 nmol/l $\approx$ 0.078 μ g/100 ml.

TABLE II—Similarity of major diagnostic groupings in geriatric inpatients and outpatients

Diagnostic group	No with T3 below 1.51 nmol/l	
	Inpatients	Outpatients
Cerebrovascular	13/26	0/8
Cardiac failure or ischaemia	14/25	1/10
Arthritis*	10/14	1/4
Anaemia*	11/13	2/4
Respiratory infections	6/10	1/2
Diabetes	4/7	0/1
Renal failure	2/5	—
Others	5/7	1/1
Total	35/59 (59%)	2/20 (10%)

χ^2 tests of significance: 0.95>P>0.05 for difference in distribution of diagnostic groups between inpatients and outpatients, but P<0.005 for difference in distribution of low T3 levels between inpatients and outpatients.

*For individual groups P>0.10 for difference between any cell and mean of all cells except where 0.10>P>0.05 (Fisher's exact test).

subdivided (table I). Finally, the distribution of major diagnostic groups was similar in the inpatients and outpatients (table II), and low T3 levels were evenly distributed statistically among diagnostic groups.

Serum T3 and T4 levels—Despite the lack of correlation between low T3 levels and clinical factors serum T3 was noticeably reduced in the inpatients (fig 1, table III); 35 (59%) were below the normal adult range and only one was just above. In contrast, in the outpatients the mean serum T3 level was not reduced. Serum T4 levels differed from T3 in two respects. There was less difference between inpatients and outpatients, and the mean in both groups was higher than in the normal people (fig 2, table III). T4 levels above the normal range were found in 7 (12%) of the inpatients and 6 (30%) of the outpatients.

FIG 1—Serum total T3 and albumin and TBG levels. O = Geriatric outpatients. ● = Geriatric inpatients. ■ = Normal people. Dashed boxes represent normal limits (points not shown for albumin to aid clarity).

Correlation coefficients—T3 with TBG: normal people $r=0.66$, $0.01>P>0.001$; outpatients $r=0.56$, $0.05>P>0.01$; inpatients $P>0.05$. T3 with albumin: inpatients $r=0.26$, $0.05>P>0.01$; others $P>0.1$. Regression line of T3 on TBG in normal people $y=0.208x+0.046$.

Conversion: SI to traditional units—T3: 1 nmol/l $\approx$ 0.65 ng/ml.

Serum TBG and albumin levels—Mean serum TBG levels were increased in both groups of patients (table III); 19 (95%) of the values in the outpatients and 48 (83%) of those in the inpatients were above those found in the younger, normal people. No patient had a subnormal level of TBG. There was poor correlation between T3 levels and TBG

and only a partial one between T4 and TBG in the geriatric patients, although there were good correlations in the normal people (fig 1). Serum albumin levels of 30 g or less per l were found in 23 (39%) of the inpatients and 8 (40%) of the outpatients (figs 1 and 2). This contrasts sharply with the selective distribution of low T3 levels among inpatients. Fig 1 shows that T3 is generally lower in the inpatients whatever the protein levels.

FT3I and FT4I—These indices followed the total levels of T3 and T4 in general. FT3I was significantly lower in inpatients, while among outpatients it was normal. FT4I was significantly increased in both groups (table III).

TSH levels in euthyroid patients—The mean basal TSH level in the geriatric patients was significantly lower than in the normal people (table III).

FIG 2—Serum T4, TBG, and albumin levels. Key to symbols as in fig 1. Correlation coefficients: T4 with TBG—normal people: $r = 0.74$, $0.01 > P > 0.001$; outpatients: $P > 0.05$; inpatients: $r = 0.29$, $0.05 > P > 0.01$. Correlations with albumin not significant at 5% level. Regression line of T4 on TBG in normal people $y = 19.6x + 86$.

Conclusions

Although T3 levels fall with age,¹²⁻¹⁴ the reduction in our patients went far beyond this. Clearly the low T3 levels in no way indicated the presence of hypothyroidism as judged by T4 and TSH levels. The prevalence of hypothyroidism with raised TSH levels in our sample (two patients) was comparable with that in a large population survey.¹⁵ We disagree with reports that thyroid disease is prevalent (5% or more of cases) in the elderly.²⁻⁴ Based as these reports largely were on tests such as measurement of protein-bound iodine, we believe they serve to emphasise the pitfalls of reliance on measurement of a single thyroid hormone in geriatrics, even when FT3I and FT4I are taken into consideration. Subnormal or borderline FT4I was found in several patients with low T3 who would have been mistakenly diagnosed as hypothyroid if TSH levels had not been measured. While geriatric physicians may rightly often wish to exclude hypothyroidism, clearly they should not often diagnose it, and T3 and T4 assays or even FT3I and FT4I are not helpful by themselves. We suggest that the screening test of choice is the measurement of serum TSH, the meaning of high values perhaps being clarified by a TRH test and the FT4I.

Similar remarks apply to thyrotoxicosis. We found no definite case of thyrotoxicosis, although three patients had an FT3I above our normal range and showed normal TRH responses. An FT4I up to three times the normal means was present in a third of our patients and was clearly of no diagnostic value. Even the TRH test seems equivocal in the diagnosis of thyrotoxicosis, as the TSH response to TRH may be diminished in the elderly.^{13 14 16}

Reasons for low serum T3—At the biochemical level, our results suggest that a low T3 value is mainly due to a reduction in both the bound and unbound fractions rather than to abnormalities of binding proteins or the presence of drugs or other substances affecting protein binding. We point to the need for direct measurement of unbound levels (which will be reported elsewhere). Table III shows a reduced Thyopac-3 in inpatients, despite levels of T4, TBG, and albumin similar to those in outpatients, which could as well indicate the presence of a binding inhibitor¹⁷ or reduced thyroxine-binding prealbumin.¹⁸ Such complex changes in protein binding may invalidate conventional interpretation of Thyopac-3 results. At the physiological level, a low T3 concentration may be due to impaired conversion of T4 to T3, increased T3 degradation, or impaired thyroidal T3 production due to a primary abnormality in the thyroid or reduced stimulation by TSH. Our preliminary data do not distinguish these possibilities, though T4 turnover falls with age.¹⁹ At the clinical level, we were surprised that a low T3 concentration showed virtually no correlation with body weight and little with the clinical diagnosis. This did not seem to be due to aging per se since it was not present in outpatients, showed no correlation with age in the inpatients, and represented much lower values than described previously.¹²⁻¹⁴ We are satisfied that it was not due to drugs.

"T4 euthyroidism"—Presumably the maintenance of normal to high unbound T4 levels in the presence of a low T3 level in the elderly sick is responsible for their euthyroid status. Our data may represent further evidence that circulating T3 is not always the major determinant of clinical thyroid status and that both hormones contribute to it.

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