minutes. In those cases of chronic cervicitis with Nabothian follicles two applications at the same session were more effective than one. Even when the whole lesion was not covered with the cryoprobe healing was complete without the multiple applications other workers have suggested to be necessary.

Cryosurgery is less painful than diathermy (Ostergard *et al.*, 1969; Jackson, 1972) and in the present series no patient had more than slight discomfort, which did not continue after treatment was completed. Jackson (1972) and Townsend *et al.* (1971) found that mild discomfort in the lower abdomen continued for up to three days after treatment, but this was not our experience. None of our patients noted dizziness or flushing after treatment. The incidence of postoperative bleeding reported has varied considerably. Townsend *et al.* (1971) noted spotting in 50% of patients, Jackson (1972) in 26%, and Young *et al.* (1972) had only one case of haemorrhage out of 132 patients treated. In only one of our patients was vaginal spotting noted. The incidence and duration of vaginal discharge after treatment varies but is sufficiently common and

profuse to make it necessary to warn patients and to reassure them.

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Correlation between Long-acting Thyroid Stimulator Protector Level and Thyroid ¹³¹I Uptake in Thyrotoxicosis

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Summary

Out of 50 consecutive untreated patients with diffuse toxic goitre 15 showed long-acting thyroid stimulator (LATS), 30 showed LATS protector only, and five showed neither. LATS protector was present in all the patients with LATS. Infiltrative ophthalmopathy was less common in patients with LATS protector only (40%) than in patients with LATS also (67%), but the difference was not significant. There was a correlation between LATS protector level and thyroid ¹³¹I uptake rate factor (k_1), the coefficient (r) being 0.68 ($P < 0.001$). LATS level showed no such correlation. The results support the hypothesis that LATS protector is a pathogenic thyroid stimulator in patients with diffuse toxic goitre.

Introduction

Long-acting thyroid stimulator (LATS) protector is an immunoglobulin found in the serum of patients with diffuse toxic goitre (Adams and Kennedy, 1967, 1971). It competes with LATS for binding to human thyroid extract in vitro and thus protects LATS from neutralization. It does not react with mouse thyroid homogenate, however, or stimulate the mouse thyroid in vivo. In view of these characteristics it was suggested that LATS protector is a species-specific human thyroid-stimula-

ting autoantibody (Adams and Kennedy, 1971). It has since been reported that LATS protector serum stimulates intracellular colloid droplet formation in human thyroid slices incubated in vitro (Shishiba *et al.*, 1973), and we have shown by infusion studies in normal people that LATS protector plasma does have thyroid-stimulating activity in man (Adams *et al.*, 1974).

We record here the incidence of LATS protector and LATS in a series of 50 consecutive patients with untreated diffuse toxic goitre. In addition, we looked for correlations between LATS protector level and various indices of thyroid activity, seeking evidence of a causative role for LATS protector in this form of thyrotoxicosis.

Patients and Methods

The patients were 50 consecutive untreated patients with diffuse toxic goitre. Patients previously treated by thyroidectomy or radioactive iodine and those given antithyroid drugs within the previous three months were excluded as were those in whom the thyroid scan showed one or more functioning nodules. All patients were examined by one of us (R.D.H.S.), and their eye signs were classified according to criteria recommended by the American Thyroid Association (Werner, 1969), as follows: class 0, no eye signs; class 1, lid retraction or lid lag or both; class 2, chemosis (with or without class 1 signs); class 3, exophthalmos or lid bulge or both (with or without class 2 signs); class 4, oculomotor dysfunction (with or without class 3 signs).

The thyroid uptake rate factor (k_1) of Oddie *et al.* (1955) was calculated from the uptake of ¹³¹I by the thyroid at one hour; the 24-hour uptake was also measured. The thyroid scan was obtained with a rectilinear scanner after the administration of 2 mCi ^{99m}Tc pertechnetate. The area of this thyroid scan image, measured by planimetry, was used as an index of thyroid size. Serum total thyroxine (T-4) and triiodothyronine (T-3) resin uptake were measured by competitive protein-binding radioassay. The product of total T-4 and T-3 uptake (divided by 100) was used to give a free T-4 index (Clark and Horn, 1965).

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In Dunedin the normal range for k_1 is $0.8-2.0 \times 10^{-3}$ per minute, for 24-hour uptake 15-40% of the dose, for serum total T-4 $5.6-12.4 \mu\text{g}/100 \text{ ml}$, for T-3 uptake 80-115% of the uptake by a standard pooled serum, and for the free thyroxine index $5.3-11.8$.

The major criterion used for the diagnosis of thyrotoxicosis was a raised free T-4 index. When there was doubt the serum total T-4 and T-3 uptake estimations were repeated at least once using a fresh sample of blood to minimize the possibility of laboratory error. Patients were included if the free T-4 index was greater than 15.1 (4 S.D.s. above the mean value for normal people) or if at least two of the following three criteria were satisfied: (a) the free T-4 index was repeatedly greater than 13.5 (3 S.D.s. above mean normal); (b) there was no suppression of thyroid ^{131}I uptake after the administration of $100 \mu\text{g}$ T-3 for seven days; (c) there were highly suggestive clinical features—for example, the presence of infiltrative ophthalmopathy.

Serum was obtained at the time of thyroid function assessment for assay of LATS and LATS protector. LATS was measured by the McKenzie mouse bioassay as previously described (Adams and Kennedy, 1967). If a negative or doubtful response was obtained an immunoglobulin concentrate (tenfold volume reduction) prepared by ammonium sulphate precipitation (Adams and Kennedy, 1967) was assayed in six mice for comparison with the unfractionated serum, which was also assayed in six mice. LATS was considered absent if the mean response in the mice receiving the concentrate was not significantly greater ($P < 0.05$) than the mean response in the mice receiving the serum. The mean response elicited by an immunoglobulin concentrate was divided by 6 to correct for concentration and recovery.

LATS protector was measured by determining the degree to which the test serum protected a standard LATS serum from being neutralized by a standard thyroid extract. The percentage protection was calculated as shown in table I. The lower values for LATS protector were obtained by assay of immunoglobulin concentrates, these values also being divided by 6 to make them comparable to values obtained with whole serum.

TABLE I.—Assay for LATS Protector in Serum from One Patient

Assay Material	Dose per Mouse (μl)	No. of Mice	Mean Response (% Increase in Blood ^{131}I)
LATS serum	25	4	1,063
+ Saline	475		
LATS serum	25	6	42
+ Thyroid extract ..	63		
+ Normal control serum	412	6	569
LATS serum	25		
+ Thyroid extract ..	63	6	3
+ Patients serum ..	412		
Patient's serum ..	412	6	3
+ Saline	88		

$\% \text{Protection} = (569 - 42) / (1,063 - 42) \times 100 = 52.$

Results

The findings in the 50 thyrotoxic patients are shown in table

TABLE II.—Serum LATS and LATS Protector Levels and Indices of Thyroid Function in 50 Consecutive Untreated Patients with Diffuse Toxic Goitre (Mean Values $\pm$ S.E.)

	No. of Patients	Sex	Age (Years)	LATS (% Response)	LATS Protector (% Protection)	Thyroid ^{131}I Uptake Rate Factor (k_1) (Fraction/min $\times 10^3$)	Thyroid ^{131}I Uptake at 24 Hours (% of Dose)	Free Thyroxine Index	Thyroid Size (cm^3)
LATS and LATS protector present	15	12 F.; 3 M.	44.5 ± 3.4	100 ± 3.2	—*	14.6 ± 1.4	67.4 ± 2.8	29.5 ± 2.3	22.9 ± 1.9
LATS protector only present	30	25 F.; 5 M.	44.7 ± 2.7	0	32.2 ± 3.6	11.1 ± 1.6	59.5 ± 2.3	27.3 ± 1.7	21.6 ± 1.6
LATS and LATS protector absent	5	4 F.; 1 M.	50.8 ± 5.8	0	0	2.3 ± 0.5	34.5 ± 7.4	15.0 ± 1.3	33.6 ± 2.0
Total	50	41 F.; 9 M.	45.2 ± 2.0			11.3 ± 1.1	58.9 ± 2.0	26.8 ± 1.3	23.2 ± 1.2

*LATS protector present but actual values not calculated (see text).

II, grouped according to the presence or absence of LATS and LATS protector. LATS was detected in 15 cases, LATS protector only in 30 of the remainder, and five patients showed neither LATS nor LATS protector. LATS protector was present in all patients in whom LATS was present, giving an incidence of 90% for LATS protector in the whole group. The presence of LATS in the test serum complicated the measurement of LATS protector, and, as we did not solve this problem, actual values for LATS protector in the LATS-positive group are not given.

The group of patients with LATS had a slightly higher mean k_1 , 24-hour uptake, and free thyroxine index than the group with only LATS protector, suggesting that the former patients might have had somewhat more severe disease. The five patients with neither LATS nor LATS protector differed strikingly from those in the other groups in two ways. The indices of thyroid function were much lower, being for the most part only marginally abnormal, and the mean thyroid size was considerably greater. The eye signs of infiltrative ophthalmopathy (classes 2, 3, or 4) were present in 10 of the 15 patients showing LATS (67%), in 12 of the 30 having only LATS protector (40%), and in one of the five with neither thyroid stimulator (20%).

Correlations between serum LATS protector level and indices of thyroid function, thyroid size, and class of ophthalmopathy were calculated for the group of 30 patients with only LATS protector in their serum. LATS protector level was highly correlated with k_1 ($r = 0.68$; $P < 0.001$). There was no significant correlation between LATS protector and 24-hour uptake ($r = 0.33$), free T-4 index ($r = 0.32$), thyroid size ($r = 0.22$), or class of ophthalmopathy ($r = 0.13$). The correlation between k_1 and LATS protector for these 30 patients is shown in the scattergram. Values for the five patients without either LATS or LATS protector are also included in this figure. In the patients with LATS the serum level of LATS did not correlate significantly with k_1 ($r = 0.06$) or with any other index measured.

FIG. 1—Relation between serum LATS protector concentration and thyroid ^{131}I uptake rate factor (k_1) in 35 LATS-negative patients with diffuse toxic goitre.

Discussion

Despite the increase in our knowledge and understanding of the pathogenic mechanisms present in patients with diffuse toxic goitre—particularly since the discovery of LATS (Adams, 1958) and its characterization as an immunoglobulin (Adams and Kennedy, 1962; McKenzie, 1962; Kriss *et al.*, 1964; Dorrington *et al.*, 1966)—the cause of the abnormal thyroid function in this disease has remained uncertain. The simplest explanation, and the only one which accounts for the phenomenon of neonatal thyrotoxicosis, is that there is a circulating humoral stimulator acting upon the gland (McKenzie, 1972). Thyrotrophin has been excluded from this role by the fact that its level in blood is less than normal in diffuse toxic goitre (Adams *et al.*, 1969). To many workers LATS has been unacceptable as a causative agent because it is undetectable in many cases and the level in any individual patient does not correlate with the degree of abnormal thyroid function (Volpe *et al.*, 1972). LATS protector, however, meets two criteria not fulfilled by LATS; our evidence confirms the high incidence of LATS protector in diffuse toxic goitre and shows that its serum level correlates well with early thyroid ^{131}I uptake. Furthermore, LATS protector has been shown to stimulate the human thyroid, both *in vitro* (Shishiba *et al.*, 1973) and *in vivo* (Adams *et al.*, 1974). We therefore think that in LATS-negative patients with diffuse toxic goitre LATS protector is the pathogenic agent.

The question whether LATS protector is present in every case of diffuse toxic goitre remains open. It was not found in five of the 50 patients studied, but all these were relatively mild cases with normal or only slightly raised thyroid ^{131}I uptake and large goitres. Failure to detect LATS protector in these inactive cases may have been due to assay insensitivity, but incorrect diagnosis of thyrotoxicosis or an alternative pathogenic mechanism for thyroid dysfunction are other possible explanations.

The pathogenesis of the ophthalmopathy of Graves's disease remains less well understood than the pathogenesis of thyrotoxicosis. We found no significant correlation between the class of ophthalmopathy and the LATS protector level. The highest incidence of infiltrative ophthalmopathy, however, was observed in the group of patients with both LATS and LATS protector, and the lowest incidence was in those patients in whom neither immunoglobulin could be detected. Our findings support the view that LATS protector and ophthalmopathy may be associated in Graves's disease but the relation is not a causal one.

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Respiratory Symptoms in Children and Parental Smoking and Phlegm Production

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Summary

A study of respiratory symptoms in 2,426 schoolchildren aged 6-14 years was carried out in Aylesbury, Buckinghamshire, in 1971. The prevalence of cough in the children was associated with the parents' smoking habits; prevalence was lowest where both parents were non-smokers, highest where both parents smoked, and lay between these two levels where only one parent smoked. A close association was found between parents' and children's respiratory symptoms that was independent of parents' smoking habits. There was no suggestion that exposure to the cigarette smoke generated when parents smoked had any more than a small effect upon the child's respiratory symptoms. While the sharing of genetic susceptibility between parents and children is a factor, therefore, cross infection, particularly in the families where parents smoke, is an important element in the association.

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Introduction

Norman-Taylor and Dickinson (1972) suggested that children with parents who smoke may be at particular risk from respiratory disease. These authors were not, however, explicit about the nature of the risk. They implied that exposure of children to cigarette smoke at home might increase the risk of respiratory illness. This paper reports the findings of a study in which the nature of the association between parental smoking and respiratory disease in their children was investigated.

Methods

The material was collected during a study of the prevalence of respiratory disease in schoolchildren and their parents in Aylesbury, Buckinghamshire, in 1971. The population consisted of all children aged 6-14 years attending seven schools in Aylesbury—a total of 2,598 children (1,328 boys and 1,270 girls). Data were collected on 2,426 children and their parents, a response rate of 93.4%.

A self-administered questionnaire was completed by the parents, who answered questions about their own and their