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REFERENCES

- Burke, G. (1968). *Annals of Internal Medicine*, **69**, 1127.
 Ekins, R. P., Williams, E. S., and Ellis, S. (1969). *Clinical Biochemistry*, **2**, 252.
 Field, J. B. (1968). *Metabolism*, **17**, 226.
 Fore, W., and Wynn, J. (1966). *American Journal of Medicine*, **40**, 90.
 Grayson, R. R. (1960). *American Journal of Medicine*, **28**, 397.
 Jefferies, W. McK., Kelly, L. W., Levy, R. P., Cooper, G. W., and Prouty, R. L. (1956). *Journal of Clinical Endocrinology and Metabolism*, **16**, 1438.
 Jefferies, W. McK., Levy, R. P., Palmer, W. G., Storaasli, J. P., and Kelly, L. W., jun. (1953). *New England Journal of Medicine*, **249**, 876.
 Koutras, D. A., and Livadas, D. (1965). *Nuclear-Medizin*, **5**, 256.
 Murphy, B. E. P., and Pattee, C. J. (1964). *Journal of Clinical Endocrinology and Metabolism*, **24**, 187.
 Murphy, B. E. P., Pattee, C. J., and Gold, A. (1966). *Journal of Clinical Endocrinology and Metabolism*, **26**, 247.
 Nauman, J. A., Nauman, A., and Werner, S. C. (1967). *Journal of Clinical Investigation*, **46**, 1346.
 Perlmuter, M., Weisenfeld, S., Slater, S., Wallace, E. Z., and David, M. M. (1952). *Journal of Clinical Endocrinology and Metabolism*, **12**, 208.
 Perloff, W. H., Levy, L. M., and Despopoulos, A. (1952). *Journal of Clinical Endocrinology and Metabolism*, **11**, 1495.
 Querido, A., and Stanbury, J. B. (1950). *Journal of Clinical Endocrinology and Metabolism*, **10**, 1192.
 Schneeberg, N. G., Perloff, W. H., and Levy, L. M. (1954). *Journal of Clinical Endocrinology and Metabolism*, **14**, 223.
 Scowen, E. F. (1937). *Lancet*, **2**, 799.
 Shapiro, R. (1961). *New England Journal of Medicine*, **264**, 378.
 Shapiro, R., and Man, E. B. (1960). *Journal of the American Medical Association*, **173**, 1352.
 Sönksen, P. H., Ekins, R. P., Stevens, H. G., Williams, E. S., and Nabarro, J. D. N. (1968). *Lancet*, **2**, 425.
 Tait, J. F., Cook, J. R., and Worsnop, R. (1951). *British Journal of Radiology*, **24**, 14.
 Taunton, O. D., McDaniel, H. G., and Pittman, J. A., jun. (1965). *Journal of Clinical Endocrinology and Metabolism*, **25**, 266.
 Thorén, A. (1960). *Acta Endocrinologica København*, **35**, 351.
 Werner, S. C., Hamilton, H., and Nemeth, M. R. (1952). *Journal of Clinical Endocrinology and Metabolism*, **12**, 1349.
 Wynn, J. (1967). 59th Annual Meeting of the American Society for Clinical Investigation, p. 115. Quoted by S. C. Werner and J. A. Nauman, *Annual Review of Physiology*, 1968, **30**, 213.

Thyroid Suppression Test with Serum Thyroxine Concentration as Index of Suppression

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Summary: A thyroid suppression test is suggested which relies on the change in concentration of serum thyroxine as the index of thyroid response to the administration of triiodothyronine. The test has been carried out in 16 healthy volunteers and in 27 patients referred for routine suppression tests. This index appears to be sensitive and safe and results in a reduction in the required dosage of triiodothyronine. The test can be carried out in fewer patient-visits than the commonly used suppression test; moreover, in remote areas the patient need not attend the specialist centre because the course of triiodothyronine can be given (and the serum samples obtained) locally, the samples then being sent to the appropriate laboratory for assay.

Introduction

Though Greer and Smith (1954) showed that a comparison of the 24-hour neck uptake of a tracer dose of radioiodine before and after a course of desiccated thyroid afforded a useful method of distinguishing the presence of thyroid autonomy, the suppression test as now normally applied is based on the method of Werner and Spooner (1955), who used triiodothyronine (T_3) as the suppressing agent. Variants from the original report consist in the dosage regimen selected and in the particular measurements used to assess thyroid handling of an iodide tracer. This paper reports a study in which the selected index of thyroid response to the administration of a course of T_3 is the total serum concentration of thyroxine (T_4).

Materials and Methods

The serum thyroxine was measured and the ^{131}I uptake into the thyroid was determined as indicated previously (Williams *et al.*, 1969). Twenty-seven patients were studied, those in-

cluded in the series being confined to those in whom a suppression test was in any case required on clinical grounds. The volunteers (eight men and eight women) were either our colleagues or staff members of another school of the University of London; they were all healthy and their ages ranged from 23 to 58 years. With one exception, discussed below, tracer studies were not carried out on the volunteers.

The test was conducted as follows. Radioactive iodine (^{131}I) was given orally and 24 hours later the neck radioactivity measured and the percentage uptake of the administered tracer calculated in the usual way. A blood sample was also taken at this time and the serum separated and stored in deep-freeze for later thyroxine assay. The course of T_3 was then given; in the case of patients this was usually 40 μg . every eight hours for seven days. Some of the volunteers were also given this dosage but others received 20 μg every six hours and others 40 μg . at eight-hour intervals on alternate days. Immediately after the course of T_3 a second blood sample was taken for serum thyroxine assay, and, in the patients, the residual neck radioactivity was measured before a second dose of 15–20 μCi ^{131}I was given. Twenty-four hours later the percentage thyroid uptake of tracer was again determined. Blood samples for serum thyroxine assay were obtained from the volunteers at intervals during the course of T_3 as well as after its completion.

Results

The initial serum T_4 concentration in all the volunteers was in the normal range, which in our laboratory is taken to be 45–115 ng./ml. (Ekins *et al.*, 1969). The results presented in each of the figures are expressed as a percentage of this initial concentration, taken as 100%. The serum T_4 values during and immediately following the course of T_3 fell within the shaded area of Fig. 1 in 15 of the 16 volunteers. The exception was a man aged 40. Fig. 2 shows his serum T_4 values during two courses of T_3 separated by three months. When the 24-hour uptake was used as the index, and 40 μg . T_3 was given every eight hours for seven days, only partial suppression occurred. It was subsequently discovered that there is a family

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history of thyroid disease, but the subject himself appears to be healthy. It is perhaps worth mentioning that the first tracer test on this man was vitiated by self-medication with Entero-vioform (Sönksen *et al.*, 1968) some weeks previously, which he had forgotten, though he had been questioned about iodide medication before the test was undertaken. The test was repeated in another of the volunteers after a nine-month interval, the results of the two tests being shown in Fig. 3.

Serum samples were taken from 27 patients routinely referred for suppression tests at the beginning and at the end of the course of T_3 . The results of the T_4 and ^{131}I uptake tests were consistent in 24 of these. Of the other three, one patient showed an insignificant reduction of T_4 concentration in the presence of a pronounced suppression of the 24-hour uptake. At this time there were clinical signs of toxicity, but eight months later, when there had been clinical improvement, both the T_4 and the 24-hour uptake suppressed normally.

FIG. 1.—Concentration of serum thyroxine expressed as a percentage of the initial value fell within the shaded area in normally responsive subjects during and immediately following a course of triiodothyronine varying from 120 μ g. daily, in divided dosage. FIG. 2.—Serum thyroxine values plotted as in Fig. 1: the results of two suppression tests separated by three months. This subject's ^{131}I uptake was only partially suppressed by 40 μ g. triiodothyronine eight-hourly for seven days. FIG. 3.—Serum thyroxine response in one healthy subject to each of two courses of triiodothyronine separated by nine months.

Discussion

The possibility of using the serum T_4 concentration as an index of thyroid suppression depends on the specificity of the T_4 assay in relation to T_3 . The assay system is responsive to T_3 , but the energies of reaction are such that, at the reagent concentrations used, T_3 is seven to eight times less potent than T_4 . (This ratio is not constant but depends on the actual conditions of assay selected; in practice, however, circumstances are never likely to arise in which the assay system becomes unduly responsive to T_3 .)

If we assume that the time taken for a given dose of T_3 to diffuse throughout the T_3 space (S) is small compared with the degradation rate of T_3 in the body, then the concentration of T_3 throughout S at any time t after the administration of a dose Co of T_3 is given by:

$$C_t = \frac{Co}{S} \left(\frac{-xt}{e} + \frac{-x(t-y)}{e} + \dots + \frac{-xy}{e} \right)$$

where x is the degradation constant of T_3 in the body and y is the uniform time interval between doses. If we administer 40 μ g. of T_3 eight-hourly and assume S=30 litres (based on Fisher and Oddie (1964) mean S of 31 litres) we find that the total body content reaches about equilibrium in six days, the serum concentration then being about 8 ng./ml. At this time in a healthy subject the serum concentration of T_4 should be of the order of 40–50 ng./ml., and in a subject whose thyroid activity is not suppressed it should be considerably higher. In

the T_4 assay system used this concentration of serum T_3 would be assayed as about $8 \times 1/8 = 1$ ng./ml. of T_4 , representing a T_4 overestimate of about 2%. Though an overall approximate correction of each T_4 assay result could be applied (and, in a particular case, a more exact correction would be possible), we do not feel that such correction is necessary, and the results presented here are based on the uncorrected T_4 assay results.

The significance of an apparent reduction in the concentration of serum T_4 depends on the precision of the assay, and hence the duration of the required course of T_3 to produce a significant result also depends on the assay precision. Thirty determinations were carried out on a serum sample, the mean T_4 concentration being 72.8 ng./ml., with a standard deviation of 3.8 ng./ml., or 5.2%. The mean of 18 determinations on another sample was 86.4 ng./ml., with a standard deviation of 1.95 ng./ml., or 2.3%. In every case the T_4 determinations on the series of serum samples obtained during the administration of T_3 to a particular subject were all carried out within a single assay run, so that if we accept as significant a fall in the concentration of serum thyroxine of two standard deviations (about 10%) we find that a significant fall occurs within five days in normally responsive individuals. In most of these this fall occurs in three days.

Results in normal volunteers were not dependent on T_3 dosage within the range 80–120 μ g. daily. Moreover, because it had been noted that the serum T_4 concentration did not begin to rise until at least two days after the termination of the course of T_3 , a dosage regimen of 40 μ g. at eight-hour intervals on alternate days was tried in three volunteers. The graphs of successive serum T_4 values were similar to those obtained when higher dosage was used. The results of the repeated tests shown in Fig. 2 were obtained, the first with 120 μ g. T_3 daily, the second with 120 μ g. every alternate day; in Fig. 3 in the first test 120 μ g. daily was given and in the second test 80 μ g. daily. Thus it would appear that no more than 80 μ g. T_3 daily need be given, and further studies may confirm that even less is sufficient for this test.

Four of the women volunteers were taking oral contraceptive agents at the time of the test. The results obtained differed in no way from those of the rest of the group.

Of the three patients in whom the assessment of thyroid suppression based on the tracer study differed from that based on the serum T_4 concentration, the one in whom the ^{131}I uptake was initially suppressed despite absence of response in the serum T_4 concentration, is of considerable interest. It is possible that in certain cases the thyroid gland might become autonomous vis-à-vis its secretory functions at a time before the impairment of the regulatory mechanisms governing iodine uptake. If such were the case then the use of serum T_4 concentration as an index of suppressibility could be a more sensitive index than indices based on tracer uptake measurements.

The two other patients in whom discordant results were obtained were both women. One was a young woman with a "hot nodule" whose uptake did not suppress but whose T_4 came just within the tentative limit of normal suppression. The other showed the converse: normal suppression of uptake but no suppression of T_4 concentration. She had a goitre considered as likely to be a lymphocytic thyroiditis. The goitre decreased in size dramatically as a result of treatment with thyroxine.

Since the use of the serum T_4 concentration as an index of thyroid suppressibility avoids the in-vivo use of radioactive iodine it also avoids the disadvantages inherent in iodide tracer studies. Allusion has been made to these in the preceding paper (Williams *et al.*, 1969). It also appears that a satisfactory separation of those whose thyroid gland suppresses from those whose gland does not can be obtained with a three-day to five-day course of no more than 80 μ g. daily of T_3 .

Though further studies are necessary to determine the optimum dosage regimen to maximize the diagnostic efficiency of the test, it would appear that the use of the thyroid functional index suggested would minimize the possible adverse effects of T_3 administration in the presence of thyrotoxicosis.

We would like to thank our colleagues who allowed us to carry out studies on them and the members of the consultant staff of the Middlesex Hospital who referred patients to us for investigation and so enabled this work to be carried out.

Levamisole in the Treatment of Ascariasis in Children

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REFERENCES

- Ekins, R. P., Williams, E. S., and Ellis, S. (1969). *Clinical Biochemistry*, 2, 252.
Fisher, D. A., and Oddie, T. H. (1964). *Journal of Clinical Endocrinology and Metabolism*, 24, 733.
Greer, M. A., and Smith, G. E. (1954). *Journal of Clinical Endocrinology and Metabolism*, 14, 1374.
Sönksen, P. H., Ekins, R. P., Stevens, H. G., Williams, E. S., and Nabarro, J. D. N. (1968). *Lancet*, 2, 425.
Werner, S. C., and Spooner, M. (1955). *Bulletin of the New York Academy of Medicine*, 31, 137.
Williams, E. S., Ekins, R. P., and Ellis, S. M. (1969). *British Medical Journal*, 4, 16.

Summary: Levamisole (the laevorotatory isomer of tetramisole) is a new synthetic anthelmintic. A cure rate of 91% was obtained in a series of 111 ascariasis-infected children treated with a single oral dose of the drug. The failures, who were treated with the drug a second time one week later, were all cured. In a comparative study of levamisole and piperazine citrate in a series of 100 children with ascariasis a cure rate of 92% and 90% was obtained with a single dose of levamisole and piperazine respectively, indicating equal efficacy. Levamisole is better tolerated than piperazine citrate and is virtually free of toxic effects.

Introduction

Tetramisole is a synthetic compound which has been found to possess anthelmintic properties. Chemically it is the hydrochloride of 2,3,5,6-tetrahydro-6-phenylimidazo(2,1-b)thiazole. The racemic mixture of tetramisole has been found to be effective at low dose levels against a variety of nematodes.

Clinical trials carried out in South America (Mesquita and Daher, 1966; Nascimento Filha *et al.*, 1966) and South Africa (Seftel and Heinz, 1968) showed that it is highly effective and safe in the treatment of ascariasis in man.

Further studies in rats, mice, sheep, and cattle have shown that levamisole, the laevo-isomer of tetramisole, is about twice as active as the racemic mixture, and, depending on the parasite, several times more active than the dextro-isomer (Rohrbacher *et al.*, 1967; Bullock *et al.*, 1968). In rats and mice the LD_{50} values for the two isomers and for racemic tetramisole proved almost identical (Raeymaekers *et al.*, 1967). These findings indicated that levamisole would be as effective as the racemic mixture at a lower dosage, and that the safety margin could correspondingly be increased.

It was therefore decided to conduct a clinical trial to assess the therapeutic and toxic effects of levamisole in the treatment of ascariasis in children.

Patients and Methods

The trial was carried out in two stages. The first stage was to determine the efficacy and safety of levamisole in the treat-

ment of ascariasis in children, and the second stage was to compare its effects with those of piperazine, at present the drug of choice in treating ascariasis.

Children whose stools showed ascaris ova on faecal smear examination were selected for the trial from those admitted to two wards of the Lady Ridgeway Hospital, Colombo. The stools were examined with the faecal smear technique (Beaver, 1961), a recognized method of carrying out ascaris ova counts (W.H.O., 1964).

In the first stage of the trial the effects of levamisole were determined in 111 patients, many of whom had symptoms suggestive of ascariasis, such as vomiting, diarrhoea, and abdominal pain. Four of them were drowsy and dehydrated, 22 showed evidence of malnutrition, and 12 were severely anaemic with haemoglobin levels below 7.4 g./100 ml. Eighty-one were between 2 and 9 years of age, 13 less than 2 years, and 17 over 9 years. Liver function tests were carried out before and after treatment on 14 patients, and haemoglobin estimations on 20 patients selected randomly, to determine possible hepatic and haemopoietic toxicity.

In the second stage of the trial 100 children were randomly allocated to two groups, one group being treated with levamisole and the other with piperazine. At the end of the trial there were 50 patients in each group. Table I compares the two treatment groups with regard to sex and age. Table II shows the similarity of the presenting symptoms in the patients in the two groups before treatment.

TABLE I.—Comparability of Treatment Groups with Regard to Sex and Age

		No. of Patients	
		Piperazine	Levamisole
Male		22	26
Female		28	24
Age	Under 2 years	5	4
	2 to less than 4 years	14	10
	4 to less than 9 years	24	30
	Over 9 years	7	6

TABLE II.—Presenting Symptoms and Signs

Symptoms and Signs		No. of Patients	
		Piperazine	Levamisole
Abdominal pain		9	11
Diarrhoea		18	13
Vomiting		13	16
Drowsy and dehydrated		6	5
Malnutrition		8	4
No symptoms		12	11

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