Long-term Result of Antithyroid Drug Therapy for Grave's Disease: Follow up after more than 5 years

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Synopsis

From 1955 to 1963, 159 cases of Grave's disease were treated with antithyroid drugs for more than 6 months. This report concerns the outcome of these cases in 1969. Among 159 patients treated with antithyroid drugs, the present status could be studied in 86 cases. In these 86 cases, 24 were in remission for more than 2 years after the discontinuance of antithyroid drug therapy, 4 were in remission less than 2 years after the discontinuance of antithyroid drug therapy, 1 case was still hyperthyroid, 9 cases were still receiving antithyroid drugs, 6 underwent an operation because of recurrence, and 24 underwent ^{131}I therapy because of recurrence. Remission rate after the administration of antithyroid drug for less than one year was 24%. In recurrent cases after further administration for 2 to 6 years, 10–20% of the patients experienced prolonged remission. In order to find out the factors related to permanent remission, 42 patients with permanent remission and 40 patients who failed permanent remission were compared in several factors.

From these studies, the incidence of permanent remission seems to be high in the following cases. 1) small goiter 2) short duration of symptoms 3) reduction in the size of the goiter during the treatment 4) positive suppression by thyroid suppression test at the conclusion of treatment. It was also observed that in cases in which antithyroid drug therapy was not effective after one year, further treatment for 2 to 5 years led to permanent remission in some cases. However, such a possibility is very small after more than 6 years of treatment.

The authors have 9 patients who have been taking small doses of antithyroid drugs for 5 to 12 years and working well in euthyroid conditions. Considering the shortcomings of surgery and ^{131}I therapy, this kind of treatment might be appropriate in some cases.

There are several reports on the outcome of hyperthyroidism treated with antithyroid drugs. However, the rate of prolonged remission after the discontinuance of treatment is varied in these reports. From 1955 to 1963 we treated 159 cases of Grave's disease with antithyroid drugs for more than six months. This report concerns the outcome of these cases in 1969, namely, more than 5 years after the initiation of antithyroid drug therapy.

Materials and Methods

As mentioned above, 159 cases were administered antithyroid drugs for 6 months through 9 years from 1955 to 1963. These patients were treated with these drugs on the following basis:

- (1) Patients who passed less than a half year after the onset of symptoms and whose goiters were not markedly large in size.
- (2) Patients who passed more than a half year after the onset of symptoms and whose goiters were small in size.

(3) Patients, except (1) and (2), who did not want to undergo any surgery or ^{131}I therapy.

The antithyroid drugs used were methylmercaptomidazole (Mercazole) or methylthiouracil (Methiosil). These drugs were first administered for 6 to 12 months. During these periods, the doses of drugs were adjusted at 2 to 4 weeks' intervals to maintain the euthyroid state. When recurrences occurred after the discontinuance of this treatment, the antithyroid drugs were administered again or other therapies were applied. We requested 159 patients to return to our hospital in order to learn their present status and 49 cases came to the hospital and 37 cases answered by mail, that is, the present status of 86 cases (54%) could be evaluated. Among these 86 cases, 60 cases were treated with methylmercaptomidazole, 13 cases with methylthiouracil and 13 cases with both drugs. The patients who came to our hospital underwent physical examinations and thyroid function tests, and from these results the present status was comprehensively judged. The present status of those who answered only by mail was estimated by the postal information.

Results

The present status of the above 86 patients evaluated in this way is shown in Table 1: 46 cases are euthyroid and 42 cases of this group have been euthyroid for more than 2 years after the discontinuance of treatment, and 4 cases are still euthyroid for less than 2 years. One case is still hyperthyroid, 9 cases are now undergoing medication, 6 cases were operated

Table 1. Present status of patients treated with long-term antithyroid drug therapy

(1) In remission	more than 2 years after the discontinuance of treatment	42 cases
	less than 2 years after the discontinuance of treatment	4
(2) Hyperthyroid		1
(3) On medication		9
(4) Relapse after the discontinuance operation		6
(5) Relapse after the discontinuance ^{131}I therapy		24
Total		86

on and 24 cases underwent ^{131}I therapy due to recurrence.

Among these cases, 62 patients had a relapse after the discontinuance of antithyroid drugs and the duration from discontinuance to relapse is shown in Table 2: that is, about 60% of patients had a relapse within 3 months and 94% within 2 years. If we assume that the patients who have been in remission for more than 2 years (as shown in Table 1) are patients in permanent remission, 42 cases (51%) out of 82 (4 other cases have passed less than 2 years after the discontinuance) have been in permanent remission with antithyroid drug therapy.

The duration of remission from the discontinuance of medication up to now is shown in Table 3. In 21 cases, it was more than 5 years.

The relations between the duration of administration and the prognosis in these cases are shown in Table 4. When the duration was less than one year, remission was observed in 24% of the patients. Permanent remission was observed in 18% out of 51 patients who had a relapse and were treated again with anti-

Table 2. Duration of remission before relapse

0 to 3 months	36 cases	
4 to 6 months	9	94 %
7 to 12 months	7	
1 to 2 years	6	
2 to 3 years	3	
3 to 4 years	1	
Total	62	

Table 3. Duration of remission from discontinuance of medication

2 to 3 years	7 cases
3 to 4 years	7
4 to 5 years	7
5 to 6 years	7
6 to 7 years	3
7 to 8 years	3
8 to 9 years	0
9 to 10 years	3
more than 10 years	5
Total	42

Table 4. Relationship between the duration of administration of drug and prognosis

Duration of administration	Number of cases	Remission	Relapse
within a year	82	20 (24%)	62
1 to 2 years	51	9 (18%)	42
2 to 3 years	33	6 (19%)	27
3 to 4 years	22	3 (21%)	19
4 to 5 years	16	3 (19%)	13
5 to 6 years	11	1	10
6 to 12 years	10	0	10

thyroid drug and the total period of administration was between 1 and 2 years. Further, permanent remission was observed in about 20% of those who had a relapse and were treated with repeated administration for 2 to 5 years. However, permanent remission was not observed in 10 cases who were treated with administration for more than 6 years.

Factors Possibly Related to Response

Several factors between 42 cases in permanent remission and 40 incurable ones were compared and examined.

The relations between the durations of symptoms before treatment and the rates of remission are shown in Table 5. The comparison of the treatments started within a half year after the onset of symptoms with those started in more than a half year thereafter was examined by χ^2 test and the former showed a higher rate of remission ($p < 0.5$).

No significant relation was observed between rates of remission and sex or age. Also no significant relation was observed between exophthalmos and rates of remission. (Table 6)

The relations between the size of goiters and the rate of remission are shown in Table 7. The size of goiters was estimated by palpation, and classified into small (below 30 g), medium (30–50 g) and large (above 50 g). As shown in this table, it was clearly observed that the patients whose goiters were small in size showed high rates of remission, while those whose goiters were large in size showed very

Table 5. Relations between durations of symptoms before treatment and rates of remission

Duration of symptoms	Remission	Incurable
0 to 6 months	29	19
7 to 12 months	4	9
13 to 24 months	4	6
more than 25 months	2	4

Table 6. Relations between exophthalmos and rates of remission

Exophthalmos	Remission	Incurable
+	15	20
—	27	20

Table 7. Relations between the size of goiters and rates of remission

Size of goiters	Remission	Incurable
large	1	7
medium	26	26
small	16	6

Table 8. Relations between BMR and the rates of remission

BMR	Remission	Incurable
less than +29%	6	6
+30 to 59%	22	16
more than +60%	11	14

low rates of remission ($p < 0.1$).

The relations between the basal metabolic rate and the rates of remission are shown in Table 8 and no significant relation was observed between severity judged from the rates of basal metabolism and that from the rates of remission.

The relations between the changes of the size of goiters and the rates of remission are shown in Table 9 and the patients whose goiters reduced in size under treatment were recognized as showing high rates of remission.

In 30 cases, thyroid suppression tests were performed at the time of discontinuance of

Table 9. Changes in goiters under treatment

Change of goiter	Remission	Incurable
enlarged	2	5
no change	12	16
reduced	14	8

Table 10. Relations between thyroid suppression test at the discontinuance and the rate of remission

Suppression	Remission	Incurable
Positive	12	1
Negative	4	13

treatment. The relations between the results and the rates of remission are shown in Table 10. The thyroid suppression test was performed by administering triiodothyronine in a dose of 75 γ per day for a week and by measuring the rate of 24 hr thyroidal ^{131}I uptake before and after the administration of T_3 and when the ^{131}I uptake reduced to less than 50% of that before the administration, it was designated as positive suppression. From this result, most of the patients who showed positive suppression at the discontinuance of treatment, maintained permanent remission while 3/4 cases of those who showed negative suppression had a relapse.

From the above results, permanent remission after the long-term therapy with antithyroid drugs is more likely in the following cases:

- (1) Goiters small in size
- (2) Hyperthyroidism of short duration
- (3) Reduction in size of goiters during the treatment
- (4) Positive thyroid suppression at the time of discontinuance of treatment

Among cases in which recurrences are observed after the administration for a year, a considerable number of them showed permanent remission after further administration for 2, 3 or 4 years. Therefore, in cases which relapsed after less than 1 year of administration, permanent remission must not be given up

Table 11. Duration of administration in the cases of long-term continuous therapy

Duration	Number of cases
5 to 6 years	2
6 to 7 years	2
7 to 8 years	1
8 to 9 years	1
9 to 10 years	0
10 to 11 years	2
11 to 12 years	1
Total	9

and further administrations of antithyroid drugs should be done as far as circumstances permit.

Long-term Antithyroid Drug Therapy for more than 5 Years

As mentioned above, 9 patients have been treated with antithyroid drugs for more than 5 years, and the durations of administration are shown in Table 11. These patients have been treated with a dose of 50 to 100 mg of methylthiouracil or 2.5 to 10 mg of methylmercaptoimidazole for a long term till now as their occasional discontinuance for 1 to 3 months caused a return of symptoms and they refused ^{131}I therapy or surgery.

Discussion

1) On permanent remission rates

Among the reports on the outcome of long-term antithyroid drug therapy, those cases who passed more than 4 years after the discontinuance of treatment are as follows: Solomon *et al.* (1953) reported that 56 (55.5%) of 101 patients treated with antithyroid drugs for more than 6 months reached permanent remission by the first treatment and that 15 more cases (15.2%) reached permanent remission by the second and third long-term repeated therapy with antithyroid drugs. McCullagh and Cassidy (1953) reported that 40 (67%) of 60 patients whose goiters were smaller than medium in size, were in remission 4 to 6 years after the discontinuance of anti-

thyroid drug therapy. Trotter (1961) reported the results of the following-up study on 196 cases who were selected at random and underwent antithyroid drug therapy for more than 3 years. According to these results, the present status could be ascertained in 157 cases and 70 (45%) of them were in remission more than 10 years after the treatment was discontinued, 2 (1%) showed symptoms of hyperthyroidism, 16 (10%) were administered antithyroid drugs, 41 (26%) were treated with radioiodine therapy, and 28 (18%) underwent subtotal thyroidectomy. Reveno and Rosenbaum (1964) performed antithyroid drug therapy for 6 months on 167 patients and reported that 95 cases (57%) were in remission 4 to 19 years after the treatment. Hershman *et al.* (1966) reported that they examined the outcome on 355 patients treated with antithyroid drug therapy for a year; the present status could be found in 176 cases, and 95 (54%) of them were in remission. Previously the authors (1959) reported that among 44 cases who passed more than 3 years after the discontinuance of antithyroid drug treatment, 19 cases (43%) were in remission.

From these results the rate of permanent remission after the long-term antithyroid drug therapy can be estimated as 45 to 70%. However, Solomon *et al.* (1953) and Hershman *et al.* (1966) reported that the administration of antithyroid drugs for a year brought 50% remission rate after the discontinuance and Trotter (1961) reported 45% remission rate after the administration for 4 to 45 months, while the authors' results show only 24% after the administration of drugs for a year and 51% after the administration of drugs for 1 to 6 years. Recently, Niitani *et al.* (1969) reported that the administration for a year brought only 24% of 84 patients in remission after the discontinuance and further repeated administrations in 2 to 3 times achieved 50% remission rate. These results were well in accord with the authors' result and those of the administration for a year showed fairly lower values than those reported in the U.S.A. This fact

may indicate the peculiarity of patients in Japan. However, the possibility that the patients reported by Solomon *et al.* (1953) and Hershman *et al.* (1966) may have contained comparatively more cases who were apt to reach the prolonged remission even if the patients of hyperthyroidism were nonselectively treated with antithyroid drug therapy, cannot be denied. Further studies are necessary on this point.

2) On cases possibly related to response

On cases possibly related to response, Solomon *et al.* (1953) stated that the patients whose goiters were small in size or reduced in size during the treatment were apt to be in permanent remission and McCullagh *et al.* (1953) treated only the patients whose goiters were smaller than medium in size and reported on the excellent remission rate of 67%, although they did not refer to the size of goiters and they stated that the duration of administration of antithyroid drugs for more than 11 months was better in result. Reveno *et al.* (1964) stated that the patients whose goiters were small, those in whom the duration of symptoms was short, or those who were not severely ill were apt to be in permanent remission. Hershman *et al.* (1966) also stated that the patients who passed less than a year after the appearance of symptoms and those whose goiters reduced in size were likely to be in permanent remission. The authors' previous report (1959) showed that the patients who had no exophthalmos and those whose goiters were small in size, were likely to be in permanent remission. These reports are almost in accord with the results of the authors' present study.

Cassidy *et al.* (1965) reported that in the examination of the status after 2 to 7 years on 53 patients who were put to thyroid suppression tests at the discontinuance of treatment, only 1 (5.6%) of 18 cases whose 24 hr ^{131}I uptake reduced to less than 30% showed recurrence while 25 (71%) of 35 cases whose ^{131}I uptake did not reduce to 30% showed

recurrence and that thyroid suppression tests at the time of discontinuance of treatment was of use for judging the outcome after the discontinuance of treatment. Alexander *et al.* (1969) reported that they performed similar examinations on 36 patients and followed the outcome for more than 5 months, in average, 10 months. They found only 2 cases of recurrence out of 25 in which the suppression was positive while they found recurrences in all of 11, in which the suppression was negative. The recurrence occurred after 1 to 10 months. In the present report, recurrence was observed only in 1 of 12 cases in which the suppression test was positive, while it was observed in 11 of 15 cases in which the suppression test was negative. Hales *et al.* (1969) also reported that those patients whose radioiodine uptake did not become suppressible during the antithyroid drug therapy had much more frequent recurrence after the discontinuance of therapy. From these results this test seems to be useful for judging the time of discontinuance of the drug therapy.

3) *On the continued use of antithyroid drugs for many years*

The authors have reported on 9 cases who maintained euthyroid condition for 5 to 12 years taking antithyroid drugs almost continuously. Although there is a problem of side effects in using antithyroid drugs, there is almost no appearance of them after the administration of the drug for more than 6 months. Trotter *et al.* (1961) also reported 16

cases who had been given antithyroid drugs for more than 10 years. Therefore, considering the shortcomings of surgery and ^{131}I therapy, semipermanent administration of antithyroid drugs can be one method of treatment in some cases.

References

- Alexander, W. D. (1969). *Metabolism*, **18**, 58.
Cassidy, C. E. (1965). *J. Clin. Endocrinol.*, **25**, 155.
Hales, I., J. Stiel, T. Reeve, T. Heap and J. Myhill (1969). *J. Clin. Endocrinol.*, **29**, 998.
Hershman, J. M., J. R. Givens, C. E. Cassidy and E. B. Astwood (1966). *J. Clin. Endocrinol.*, **26**, 803.
McCullagh, E. P. and C. E. Cassidy (1953). *J. Clin. Endocrinol.*, **13**, 1507.
Niitani, H., S. Iino, K. Hayashi, T. Watanabe, K. Iigatani, K. Yuri, T. Ohno, M. Miyamoto and Y. Ban (1969). Presentation at 66th Meeting of Japan Internal Medicine Association.
Reveno, W. E. and H. Rosenbaum (1964). *Ann. Intern. Med.*, **60**, 982.
Shizume, K. (1959). Proc. of the General Assembly of the Japan Med. Congress, **1**, 847.
Solomon, D. H., J. C. Beck, V. P. VanderLann and E. B. Astwood (1953). *J. Am. Med. Assoc.*, **152**, 201.
Trotter, W. R. (1961). *Proc. Roy. Soc. Med.*, **54**, 869.