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ORAL CONTRACEPTIVES AND THROMBOEMBOLIC DISEASE: EFFECTS OF LOWERING ŒSTROGEN CONTENT

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Summary The introduction of low-œstrogen oral contraceptives in Sweden and the concomitant disappearance of high-dose preparations did not result in a lowering of the mortality of fertile women from thromboembolic disease. Morbidity due to thromboembolism seems to have fallen, and the number of thromboembolic incidents reported to the Swedish Adverse Drug Reaction Committee decreased dramatically. The decrease was due exclusively to a reduction in venous thromboembolic disease: the frequency of arterial complications (cerebral and coronary) remained constant.

Introduction

THE Swedish experiences of oral contraceptives of the combined type with regard to thromboembolism during the period 1965–70 have been presented previously.[1] After the observation, published in 1970,[2] of a positive correlation between the dose of œstrogen and the risk of thromboembolic disease, recommendations were issued in Sweden for the use of oral contraceptives with as low an œstrogen content as possible. New low-œstrogen contraceptives were introduced and the high-dose preparations gradually disappeared. The purpose of the present investigation was to see whether this change has been followed by a fall in the prevalence of thromboembolic disease in fertile women.

Methods

To facilitate comparisons with the previous study,[1] whenever possible the same pattern has been followed for the analyses. The statistics studied are not all from the same period, but there is considerable overlap. The differences are unlikely to influence the results.

Sources of Statistics

Four sources were used:

I. Official mortality statistics.—The number of deaths from thromboembolism among men and women aged 15–44 years in Sweden during 1975–77 has been received from the Central Bureau of Statistics. The following diagnoses from the 1965 revision of the International Classification of Diseases (ICD) have been included: 321 (intracranial phlebitis), 377 (central-vein thrombosis of the eye), 410 (myocardial infarction), 432–438 (intracranial thromboembolic disease), 444 (arterial embolism), 450–451 (venous embolism), 452 (portal-vein thrombosis), and 453 (thrombophlebitis). The number of deaths during 1975–77 has been compared with the corresponding figures for 1961–63 and 1966–68. Mortality figures were available for the 5-year period 1973–77, but only figures for the 3-year period 1975–77 have been included in table I and used for comparisons with earlier 3-year periods. The figures for the remaining 2 years, 1973–74, were identical to those shown in fig. 1.

II. Official morbidity statistics.—These have been obtained from the hospital record linkage system of the Uppsala region, covering 1·2 million inhabitants (15% of the Swedish population). This system, run by the National Board of Health and Welfare, registers all hospital discharge diagnoses. A retrospective study was made of the medical records (n=459) of all women aged 15–44 who had been admitted to hospital for any of the diagnoses given above. A primary exclusion (n=213) was made of all those who in the computer lists were shown

Diagnosis (with ICD numbers)	Men			Women		
	1961-63	1966-68	1975-77	1961-63	1966-68	1975-77
		p<0 05				
Cerebral thrombosis (433, 434, 435–438)	16 (1 0)	31 (1 6)	25 (1 5)	16 (1 1)	21 (1 3)	21 (1 3)
					p<0 01	
Myocardial infarction (410)	265 (17 0)	271 (16·7)	283 (16 7)	25 (1 6)	50 (3 2)	57 (3·5)
					p<0 05	
Arterial thrombosis (444)	5 (0·3)	2 (0 1)	4 (0 2)	8 (0 5)	1 (0 1)	3 (0 2)
Deep venous thrombosis (pulmonary embolism included) (450, 451, 453)	13 (0 8)	23 (1 4)	15 (0 9)	12 (0 8)	23 (1 5)	24 (1 5)

Fig. 1—Deaths from thromboembolic disease in Sweden, men and women aged 15–44.

Figures in parentheses are deaths per 100 000 in the respective age groups.

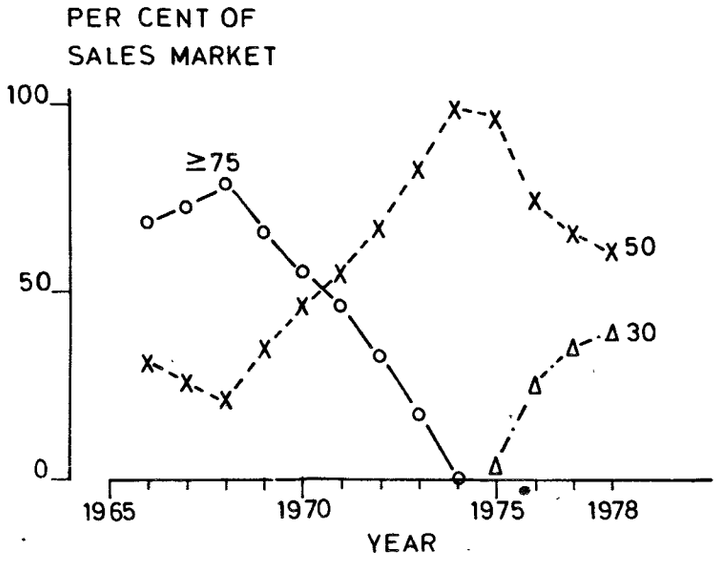

Fig. 2—Market share for high-œstrogen (⩾ 75 μg) and low-œstrogen (50 and 30 μg) oral contraceptives, 1966–78.

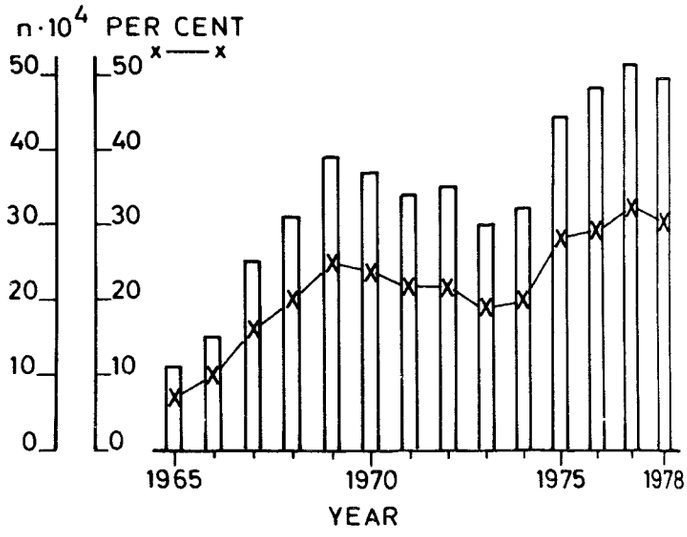

Fig. 3—Number of women aged 15–44 using oral contraceptives. Absolute numbers (n×10⁴) and per cent of total number.

Numbers calculated from sales figures, assuming that all sold pills were used for 13 cycles per year.

to have additional discharge diagnoses of disorders that in themselves might cause or predispose to thromboembolism, such as valvular heart disease, hypertension, and recent surgical interventions. A secondary exclusion (n=70) was made of those who were pregnant or had given birth within 6 weeks, had been bedridden, or had been given œstrogen therapy for other reasons than contraception. Patients with superficial thrombophlebitis were also excluded. 176 patients remained. 73 of these were free from other disease, and 103 had some disease that might predispose to thromboembolism (e.g., diabetes, malignancy, infections). These will be analysed as a "total" group (n=176) and a "clean" group (n=73). Owing to technical difficulties with the computer the figures for 1977 were incomplete. The morbidity study therefore was restricted to a 4-year period, 1973–76.

III. Adverse-drug-reaction reports.—All reports on thromboembolism in women on oral contraceptives received by the Swedish Adverse Drug Reaction Committee during the years 1973–77 were analysed. A report was accepted only if a cause-and-effect relationship between intake of the drug and the ensuing reaction had been established by the Committee. Adverse drug reactions reports were available for 1966–78.

IV. Sales figures.—Total sales figures were obtained from Swedish Drug Statistics Ltd and regional sales figures from the prescription study of the National Corporation of Pharmacies.[3] Sales figures were available for 1966–78 and prescription data for 1975–78. Total sales figures were used on the assumption that all tablets sold were consumed and used for 13 cycles per year.

Statistical Methods

Chi-square methods were used to test differences in numbers of reactions, deaths, &c. For comparisons of risk ratios Miettinen's simple interval estimation of risk ratios was used.[4]

Results

The decline in the use of the high-dose preparations and the rise of the low-œstrogen brands is shown in fig. 2. In 1974 the high-œstrogen preparations disappeared from the market, being replaced first by the 50 μg and later to a large extent by the 30 μg preparations. Progestagen-only and sequential preparations have accounted for only a small proportion of sales throughout the period under study.

There was a slight reduction in the use of oral contraceptives in Sweden around 1970, but sales figures rose again thereafter (fig. 3). Today approximately 30% of fertile women in Sweden use oral contraceptives.

Mortality

The number of men and women aged 15–44 dying from thromboembolic disease in Sweden during three separate 3-year periods, is given in fig. 1. No changes have taken place since 1966–68.

Morbidity

The number and sites of the thromboembolic episodes are given in fig. 4. The distribution between venous and arterial thromboembolism is exactly the same as that shown by the adverse drug-reaction reports (see below).

Fig. 5. presents the number of women admitted to hospital with thromboembolic disease during two 3-year periods (1966–68 and 1974–76) and the estimated numbers of users and non-users, respectively, of oral contraceptives in the same area of Sweden. During both periods there was a highly significant difference in morbidity from thromboembolic disease between users and non-users ($p<0{\cdot}001$). The relative morbidity, taking

Site of thromboembolism	Clean group	Total group
ARTERIAL		
Cerebral	5	29
Coronary	11	23
Others		3
VENOUS		
Deep venous thrombosis	44	96
Pulmonary embolism	7	18
Central retinal vein	6	7
Total	73	176

Fig. 4—Localisation of thromboembolic disease.

Morbidity study, women aged 15–44, Uppsala region.

Period	Users: No of patients with disease	Users: Estimated no of users (x1000)	Non-users: No of patients with disease	Non-users: Estimated no of non-users (x1000)	No information on contraception	Significance of difference between users & non-users
1966-68	46	107	20	698	3	p<0 001
1974-76	35	185	9	721	9	p<0 001

Fig. 5—No. of women admitted to hospital with thromboembolic disease, and estimated nos. of users and non-users of oral contraceptives ("clean" group, Uppsala region).

into account the increased use of oral contraceptives (fig. 3), seems to be lower during the later period. Calculation of risk ratios by Miettinen's method[4] gives figures of 14·96 for 1966–68 and 10·47 for 1974–76. This difference is not statistically significant.

The use of oral contraceptives increases up to 20 years of age and thereafter decreases almost linearally. The morbidity from thromboembolic disease follows the opposite pattern and increases strikingly with age (fig. 6) among both users and non-users. Users in all age-groups have more thromboembolic disease than non-users, and the ratio increases with age.

Adverse Drug Reactions

The reports received by the Swedish Drug Reaction Committee on thromboembolism in women taking oral contraceptives (fig. 7) show a sharp fall in the number of cases of both venous thrombosis ($p<0.001$) and superficial thrombophlebitis ($p<0.001$) between 1966–70 and 1973–77. The decrease is so large that the total number of reported thromboembolic episodes also is significantly ($p<0.001$) smaller, although there is no change in the number of reports on pulmonary embolism or arterial thromboembolic disease. The difference is even more striking when the reports are related to the increased use of oral contraceptives (fig. 8). From 1974 onwards the number of reported thromboembolic episodes per 100 000 users fell drastically. The average risk for a reported thromboembolic disorder was 25·9 in 1966–70 and only 7·2 in 1974–77. This difference is highly significant ($p<0.001$). Within the period 1966–70 the difference in risk for venous thromboembolism between high and low œstrogen preparations was statistically highly significant (fig. 9).

As already shown by the morbidity figures (see above), the risk of thromboembolism rises sharply with age in both users and non-users of oral contraceptives. As expected, the same pattern is found for thromboembolic episodes reported as adverse drug reactions in users (fig. 6). Mortality among reported cases (fig. 10) seems to remain constant. The small difference (0·9 to 0·6) is not significant.

Site of thromboembolism	Period 1966-70	Period 1973-77	Significance of difference between the two periods
VENOUS			
Deep venous thrombosis	236	130	p<0 001
Pulmonary embolism	34	32	NS
	270	162	p<0 001
Superficial thrombophlebitis	91	8	p<0 001
Central retinal vein thrombosis	6	5	NS
Total	367	175	
ARTERIAL			
Cerebral	25	21	NS
Coronary	6	8	NS
Other	1	2	NS
Total	32	31	NS
All sites	399	206	p<0 001

Fig. 7—Localisation of thromboembolic disease in women on oral contraceptives reported to Swedish Adverse Drug Reaction Committee during two 5-year periods.

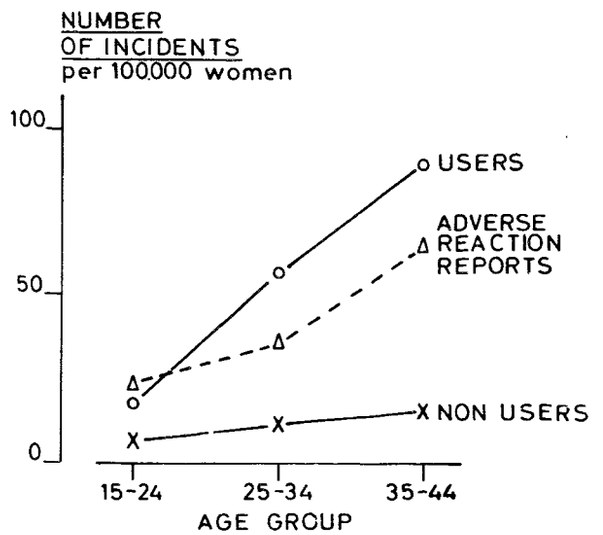

Fig. 6—Number of thromboembolic incidents in various age groups, calculated per 100 000 women.

"Users" and "non-users", respectively, refer to the morbidity study, "adverse reaction reports" to the incidents reported to the Swedish Committee.

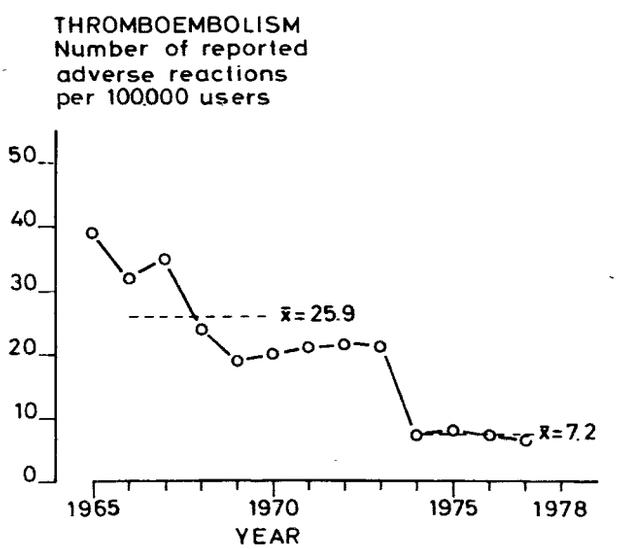

Fig. 8—Thromboembolic episodes reported to the Swedish Adverse Drug Reaction Committee, 1965–77, and calculated per 100 000 users of oral contraceptives.

Mean numbers for the periods 1966–70 and 1974–77 are indicated by broken lines.

	Low-dose	High-dose	Significance of difference (chi-square)
Venous thromboembolism	14·5	20·8	p<0·001
Arterial thromboembolism	2·5	2·0	NS
Superficial thrombophlebitis	2·9	7·7	p<0·001
All thromboembolism	20·0	30·5	p<0·001

Fig. 9—Relative risk (no. of adverse reactions reported per 100 000 users) for high and low œstrogen preparations.

ns=not significant.

Year	No. of patients	Deaths/100 000 users/year	
1966	1	0·7	
1967	3	1·2	
1968	6	1·9	
1969	2	0·5	
1970	1	0·3	
1966-70	13	0·9	
1973	4	1·3	no significant difference
1974	1	0·3	
1975	2	0·5	
1976	2	0·4	
1977	4	0·8	
1973-77	13	0·6	

Fig. 10—Deaths associated with use of oral contraceptives, from the records of the Swedish Adverse Drug Reaction Committee.

Discussion

The purpose of this analysis was to see whether the introduction of low-œstrogen contraceptive preparations had changed the pattern of thromboembolic disease in fertile women. This was achieved by comparing mortality, morbidity, and adverse-drug-reaction reports from a high-œstrogen period (1966–70) and a low-œstrogen period (1973–77). In Sweden the use of oral contraceptives fell slightly around 1970 (fig. 3) after an increased awareness of the relatively high frequency of thromboembolism and an initial enthusiasm for the use of intrauterine devices (IUD). After the introduction of the low-œstrogen pills and with the realisation that IUD also had their drawbacks, sales figures rose again. To-day, approximately 30% of fertile Swedish women use oral contraceptives.

The national mortality from thromboembolic disease has not changed since 1966–68 (fig. 1). Previously, we reported an increase in the number of fatal myocardial infarctions in young women during the early 1960s. However, subsequent[5] analysis demonstrated that the increase was probably smaller than initially suggested and that it could not be related to the use of oral contraceptives.

The morbidity from thromboembolic disease in the Uppsala region (1·2 million inhabitants or 15% of the Swedish population) seems to have fallen (fig. 5), but the difference is not statistically significant. Unfortunately, information on the use of oral contraceptives is incomplete for the periods 1966–68 and 1974–76. A skewed distribution, with relatively more users than non-users in this "no information" group, would give the decrease in morbidity a statistical significance. Thus, it does not seem unreasonable to assume that the introduction of low-œstrogen pills might have had some influence on the overall female morbidity in thromboembolic disease.

There can be no doubt, however, that the use of low-œstrogen pills has resulted in a statistically highly significant ($p<0·001$) reduction in the number of thromboembolic episodes reported to the Swedish Adverse Drug Reaction Committee (figs. 7 and 8). This finding cannot be due to changes in reporting habits. A combined analysis of morbidity material and reports to the Adverse Drug Reaction Committee enables the reporting frequency to be evaluated. For thromboembolic complications of oral contraceptives it has been found to be 25% (range 18–50% for various types of thromboembolic disease). This agrees with previous results from five independent Swedish studies,[6,7] in which an average reporting frequency of 31% (range 25–34%) was found. And the total number of reports to the Swedish committee has risen from 600 in 1966 to above 2200 in 1978.

The fall in reported thromboembolic episodes followed the disappearance of the high-œstrogen pills (fig. 8). In 1973, when the sales of high-œstrogen pills were low (17% of the market), 31% of the registered thromboembolic complications had nevertheless been caused by high dose preparations. This probably means that many women finished their year's supply of high-dose pills before switching to the new type. After Jan. 1, 1974, when the sales of high-dose preparations stopped, there appears only an occasional report on high-dose contraceptives. Thus, 1973 is to be regarded as an intermediate year, during which both high and low dose pills were used, high dose preparations probably more than corresponds to sales figures. The average number of reported thromboembolic complications per 100 000 consumers fell from 25·9 per year during 1966–70 to 7·2 during 1974–77—i.e., a highly significant ($p<0·001$) reduction to below 30%. This means that we can talk of a true dose-effect curve—a reduction of œstrogen content to approximately 50% leads to a reduction of complication rate to 30%.

The reduction in number of thromboembolic episodes reported to the Adverse Drug Reaction Committee was restricted to venous complications; there was no change in the frequency of arterial complications. This could mean that the influence of the oral contraceptives on arterial thromboembolism is even smaller than suspected or that the arterial thromboses would have occurred even without the use of oral contraceptives. The influence of such factors as changes in prescribing habits and increased knowledge about risk groups is impossible to evaluate.

An attempt to use the morbidity statistics to evaluate the influence of cigarette smoking on contraceptive-induced thromboembolism failed because the group with information lacking on both contraception and smoking habits was too large.

The use of oral contraceptives—even the low-œstrogen preparations—carries a significantly increased risk for thromboembolic disease. Users in all age groups get more thromboembolic disorders than non-users. The difference in the youngest age group is not significant, but both the risk and the difference increase

with age, the difference becoming highly significant in women aged 25 and over.

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REFERENCES

1 Böttiger LE, Westerholm B. Oral contraceptives and thromboembolic disease. *Acta Med Scand* 1971; **190:** 455–63.
2. Inman WHW, Vessey MP, Westerholm B, Engelund A. Thromboembolic disease and the steroidal content of oral contraceptives. A report to the Committee on Safety of Drugs. *Br Med J* 1970; ii: 203–09.
3. Kristoferson K, Wessling A. Tre års receptundersökningar (A three-year prescription study). *Svensk Farmaceutisk Tidskrift* 1977; **61:** 309–16.
4. Miettinen OS. Simple interval estimation of risk ratio. *Am J Epidemiol* 1974; **100:** 515–16.
5. Böttiger LE, Westerholm B. Hjärtinfarkt hos yngre kvinnor—finns samband med p-piller? (Myocardial infarction in young women—is there any connection with the use of oral contraceptives?) *Läkartidningen* 1972; **69:** 3649–52.
6. Böttiger LE, Westerholm B. Drug-induced blood dyscrasias in Sweden. *Br J Med* 1973; iii: 339–43.
7. Westerholm B. Unpublished observations, reported at the international symposium on epidemiological evaluation of drugs, Milan, 1977.

PREDICTION OF RELAPSE IN HYPERTHYROID GRAVES' DISEASE

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Summary Within a year of stopping a 6-month course of carbimazole treatment 41 of 65 patients (63%) with hyperthyroid Graves' disease had a recurrence of their hyperthyroidism. By combined analysis of the HLA-DRw3 status and the level of thyrotrophin-receptor antibody at the time of drug withdrawal relapse or remission could be predicted in 62 of the 65 patients.

Introduction

A MAJOR problem in the management of patients with Graves' disease is to predict which patients will relapse after treatment with antithyroid drugs. Relapse is more common in patients who at the end of drug therapy still show loss of thyrotrophin (thyroid-stimulating hormone, TSH) control of thyroid function[1] or the presence of antibodies which interact with the TSH receptor.[2,3] Furthermore, relapse tends to occur in patients with certain HLA specificities (HLA-B8 and Dw3).[4,5] However, these analyses have proved to be only modest predictors of disease course, and in this paper we examine the combination of HLA assessment and TSH-receptor-antibody measurements as a means of predicting relapse. Our study suggests that this may well be a useful means of assessing the course of Graves' disease.

Methods

65 unselected patients with hyperthyroid Graves' disease (51 women, 14 men; mean age 42 years) were studied. Diagnosis was made on the basis of clinical assessment, elevated serum thyroxine (T4),[6] failure of the serum TSH to respond to thyrotrophin-releasing hormone,[7] and diffuse thyroidal uptake on a technetium-99m scan. Patients were treated with carbimazole (45 mg daily) supplemented with thyroxine (0·15 mg daily) after 6 weeks, and the combined therapy was continued for a further 18 weeks. The patients were then followed at regular intervals for at least 12 months. Antibodies interacting with the TSH receptor were measured by the method of Smith and Hall.[8] Results were expressed as % inhibition of labelled TSH binding to human thyroid membranes. Studies on 67 healthy control subjects indicated that inhibition values of greater than 20% represented the presence of detectable TSH-receptor-antibody activity.

All patients were typed for HLA A and B locus antigens. The presence of the HLA-DRw 2,3,4, and 7 antigens was assessed with the standard N.I.H. lymphocytotoxic test,[9] using sera which were used in the 8th Histocompatibility Workshop or standardised against workshop specificities. The frequencies of HLA A and B loci in the local white population were established in 325 healthy unrelated subjects and DRw antigens in 135 subjects.

The statistical significance of the HLA-DRw3 associations with Graves' disease and its recurrence after a course of treatment were determined by the χ^2 test and were not corrected for the number of antigens tested. Student's t test was used for all other statistical analyses. Relative risk was calculated as described by Svejgaard et al.[10]

Results

TSH-receptor Antibodies

Receptor-antibody activity was detected in 49 (75%) of the patients before therapy and in 25 (38%) immediately after drug withdrawal (see figure). The mean ±SEM level was 46±4% inhibition of TSH binding before treatment and 24±3% after 6 months. The difference between these two values was highly significant ($p<0·001$).

In the 12 months following withdrawal of therapy 41 (63%) patients relapsed (see figure). The mean receptor-antibody level in the relapse group immediately after treatment was 33±4%. This was significantly greater than the mean level of 10±1% in the remission group ($p<0·001$). Of the 25 patients who were receptor-antibody positive immediately after drug withdrawal only 1 did not relapse (see table), and the relative risk of relapse[10] in patients who were receptor-antibody positive at this stage was 32.

DRw3-positive Patients

29 (45%) of the 65 patients were DRw3 positive, compared with 27 (20%) of the 135 control subjects. This difference was statistically significant ($\chi^2=13·2$; $p<0·001$). There was no significant difference between the pre-treatment serum T4 levels in the DRw3 positive and negative patients ($p>0·5$). The relative risk of DRw3-positive patients developing Graves' disease was 3·2. All but 2 DRw3-positive patients relapsed within 12 months of withdrawal of antithyroid-drug therapy (see figure). Of the 36 DRw3-negative patients, 14 relapsed.

The association between the presence of DRw3 and relapse (see table) was highly significant ($\chi^2=20·3$; $p<0·0001$) and the relative risk of a DRw3-positive pa-