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Recurrent Vital Depressions

A Follow-up Study of 56 Female and 28 Male Patients

J. D. VAN SCHEYEN

Hospital "Gasthuis", Middelburg (The Netherlands)

INTRODUCTION

The activity of tricyclic antidepressants in a vital depressive phase can be regarded as a therapeutic asset. In this study the diagnosis of vital depression (vital depressive syndrome, roughly equivalent to the endogenous depression of the Anglo-American literature) was established on the basis of the diagnostic criteria described in detail by Van Praag (*21*).

That a vital depression is sometimes ultimately recognizable as a (sometimes frequently) recurrent condition is a problem of importance with regard to therapy. Only a follow-up study over a longer period can give more information on this question. Such a study can establish whether more systematic antidepressant medication exerts any influence, favourably or unfavourable, on the recurrence tendency. These were some of the basic considerations of the present study. In addition there was the impression that — considered over a period of several years — more systematic treatment with antidepressants was associated in a relatively large number of patients with an increase rather than a decrease in the rate of recurrence. The antidepressants used in this study were, in order of decreasing frequency of use: amitriptyline (Tryptizol), imipramine (Tofranil), dibenzepin (Noveril) and chlorimipramine (Anafranil).

PATHOGENESIS OF VITAL DEPRESSION

SIGNIFICANCE OF PSYCHOGENIC AND HEREDITARY FACTORS

Discussing the pathogenesis of this type of depression, it can be maintained with Van Praag (*21*) that the vital depression syndrome is an aetiologically non-specific syndrome. In many cases its development would seem to be determined in part by endogenous factors. An argument to support this is, for example, the so-called 'unmotivated' depressiveness in this syndrome, and the familial hereditary taint which is often involved.

On the other hand there are psychogenic vital depressions, *i.e.* syndromes which commence as psychogenic depression but, after some time, degenerate (so to speak) to

vital depression (*21, 30*). It can be agreed with Weitbrecht (*30*) that a more exact definition of the influence of the psychogenic factors is as yet quite impossible. However, the literature (*24, 26, 30*) shows that psychogenic factors may have had a provocative effect in some 20% of larger series of patients with vital depressions. Moreover, the possible influence of psychogenic factors can be related to the premorbid structure of the patient with a vital depression. Earlier theories of Kretschmer on this subject are no longer widely accepted. The views of Tellenbach (*27, 28*) and of the Japanese investigator Shimoda mentioned by him, are more popular today. Tellenbach introduced the concept of the "melancholic type" with, as principal characteristics: excessive demands on self, compulsive orderliness, strict conscience, high level of achievement with on the other hand the constant awareness (guilt feeling) of not achieving that which is demanded or desired from self. Kraus (*15*) characterized this predepressive attitude as statothymia; an essential feature of this type is that thoughts, but particularly affects, can have abnormally prolonged after-effects, the patient being unable to dissociate himself from mostly affectively coloured experiences ('eine abnorme Neigung an Gedanken und Gefühlen kleben zu bleiben').

It seems useful to establish whether in patients with a vital depression there is indeed a premorbid structure of this kind. In fact, little is known also about the exact significance of hereditary factors. Stenstedt (*25*) and Zerbin-Rüdin (*31*) have pointed out that the morbidity risk with regard to occurrence of endogenous depressive phases is 10–15% in relatives of patients with a manic–depressive psychosis. Stenstedt emphasized that no unmistakable genetic rules can be demonstrated either in the bipolar psychosis or in the unipolar recurrent vital depression. Angst and Perris (quoted by Zerbin-Rüdin) suspected that an X-chromosomal hereditary factor may be of importance in recurrent endogenous vital depression: their series of patients included no male patients who had acquired the 'predisposition' via the father. For all that it is obvious that no definitive conclusions can as yet be formed concerning the aetiology of recurrent vital depression: the neurobiochemical aspects, the study of which is still opening up new perspectives, are not within the scope of this article.

RECURRENCE TENDENCY OF THE VITAL DEPRESSION

A problem which is important and often difficult in particular with regard to therapy, is the recurrence (the intermittent course) of vital depression. On the other hand there are undoubtedly patients who experience such a depression only once. Schipkowensky (*24*) reported that in the older literature the percentage of patients with a single depression varies rather widely: from 12% to 58%; he himself found that 22% of 202 male and 15% of 235 female patients experienced the depression only once. Taschev (*26*) found an intermittent course in 47.5% of a group of 372 patients. Age proved also to be of significance in this respect: 75% of patients with recurrent depressions and 75% of those with a single depression were over age 40. Of the patients with a first depressive phase, 65.8% were older than 50. It was established that recurrences could

be expected in 12% of patients whose first depressive phase occurred before age 30. Patients under 40 had experienced an average of two depressive phases; in age group 40–50 this average was 2.31, and in patients over 50 it was 2.5. The majority of the relevant publications show that—particularly in larger groups of patients with vital depressions—there is always a marked female predominance (generally a ratio of 2:1).

As regards the possible characteristics of the recurrent type, there are indications that the recurrences are not quite random. Angst *et al.* (*1*) studied this aspect in 1584 patients; they divided the recurrent course into a number of cycles, one cycle being the interval between the beginning of a vital depressive phase and the beginning of the next (including the 'free interval').

The advantage of this method is that the duration of the depressive phase as such need not be directly taken into account (this duration is known to vary rather widely). In the abovementioned 1584 patients the first phase was found to occur mostly between age 40 and age 60.

It was also found that the cycle duration depended on the age at which the first phase had occurred, age as such, and the number of cycles already completed. A time analysis of the entire group of patients in 5-year periods showed that the annual number of cycles during the first 5-year period was 1, 1, 2, 3 and 7, respectively. This means that, generally, the duration of each subsequent cycle was about 20% less than that of the preceding one. There was therefore an unmistakable increase in the number of cycles, *i.e.* more recurrences, at an increased age, but a decrease after age 60. Similar findings were reported by Kielholz (*13*), Taschev (*26*) and Isaakssen (*10*).

Particularly in evaluation of therapeutic results it is of importance to have some impression of the duration of a vital depressive phase to be expected. Matussek (*17*) studied the duration of endogenous depressive phases in 132 female and 112 male patients, none of whom had received ECT or antidepressant medication. These patients experienced a total of 577 depressive phases. The phase duration did not exceed 7 months in 75% of cases. Male patients more frequently showed longer, but also more frequently shorter phases; the female patients showed more frequently recurrent phases.

THERAPY AND RECURRENT COURSE

Vital depressions are the indication par excellence for antidepressant therapy. But this general rule cannot conceal the fact that this therapy fails to produce an acceptable degree of improvement in a relatively large percentage of cases (30% according to Kielholz (*13*)). Improvement or cure can often be achieved by ECT, however. The investigations of Greenblatt *et al.* (*5, 6*) and Zung (*32*) have shown that the cure rate in patients treated by ECT was substantially higher, and that the cure was generally achieved more quickly. Similar results were reported by Daily (*4*) and Kalinowsky (*11*). Given adequate determination of indications, even more favourable results seem obtainable by a combination of antidepressants and ECT. In a group of 168 patients

given this combined treatment, Heinrich *et al.* (*7*) reported failure in only a very small percentage of cases: 1.7%.

The remission rate in a group of patients treated exclusively with antidepressants was 80%. Experience with antidepressant medication shows, moreover, that in patients with recurrent vital depressions the effect of treatment was less marked in each subsequent depressive phase, so that ECT was ultimately unavoidable. ECT should certainly also be resorted to in patients who insufficiently respond to long-term antidepressant medication (3–5 weeks). This aspect has also been discussed by Scheid (*23*) and Van Praag (*20*). In some cases antidepressant medication alone produces no acceptable result until after 4–5 months. This may be a sham therapeutic effect, for in these cases a spontaneous phase of recovery may well have ensued during the long period of medication. Be this as it may, it should always be borne in mind that even a mild vital depression gives the patient much distress, and that the primary objective of therapy should be to eliminate the depression as quickly as possible. There remains the question of a possible relationship between antidepressant medication and the recurrent course.

As already indicated, the risk that a vital depression in a given patient may become recurrent is not inconsiderable. Bearing this in mind, the criteria for adequate therapy are therefore in fact twofold: to shorten the depressive phase as such as much as possible, and to prevent further recurrences. As regards the first objective, there are indications that real shortening or arrest of an (endogenous) vital depressive phase can be effected only with the aid of ECT; with antidepressants, one can achieve only what might be described as a 'tiding over'. This implies that antidepressant medication must be continued for some considerable time: at least 8 months. Short-term medication carries a high risk of rapid recurrence or re-manifestation of a depression which in fact is still present. This was pointed out as early as 1964 by Kielholz and Pöldinger (*12*) and later also by other investigators, *e.g.* Schipkowensky (*24*).

One might agree with Hofman *et al.* (*8*) that treatment (ECT and/or antidepressant medication) can influence the depressive phase as such but cannot really affect the endogenous depressive disease process—a process of which a recurrent course can be an essential characteristic.

This view raises the question whether recurrences might perhaps be prevented by a maintenance dose of antidepressants. The data in the relevant literature seem to indicate that this is not the case; on the contrary, there are indications that more protracted antidepressant medication may in fact produce a paradoxical effect: increased recurrence rate and reduced cycle duration.

This would also apply to patients whose depressive phases as such can be adequately treated with antidepressants. Hoheisel (*9*) made a catamnestic study of 64 patients older than 50 and 24 patients younger than 50, who experienced a total of 251 endogenous depressive phases. In the older group the 'free interval' prior to antidepressant medication averaged 28.6 years; treatment at that time largely consisted of ECT. After introduction of antidepressant medication the average duration of the free interval had become 4.6 years. The corresponding figures for the younger group were 14.5 and

4.6 years. Hoheisel therefore contended that antidepressant medication causes quicker recurrence. On the other hand there is the fact that in a number of cases recurrences can be treated without hospitalization, specifically with antidepressants, and sometimes by increasing the already prescribed maintenance dose.

According to Till *et al.* (*29*), vital depressions treated by long-term antidepressant therapy show an unmistakable change in their course. This change was characterized by them as 'chronification', which can become manifest in three different ways: an asymptomatic course upon continuous administration of larger doses of antidepressants over a period exceeding 18 months, an only partial cure in response to antidepressants, or an alternating course with frequent alternation of mildly depressive and mildly hypomanic phases.

The number of patients with a genuine phasic course was thus reduced. Schipkowensky *et al.* (*24*) likewise expressed the suspicion that the 'tendency to alternate' can increase in response to continued antidepressant medication, thus causes a pharmacogenically determined change to a more chronic course. Angst *et al.* (*2*) found that, during long-term maintenance therapy with imipramine, the cycle duration was reduced (recurrence rate increased): chronic administration of an antidepressant has no prophylactic effect (according to these authors, this does not apply to lithium carbonate propylaxis).

Hofman *et al.* (*8*), however, found no significant difference in recurrence rate during the 10-year period following the first depressive phase, between a group of 75 patients mostly treated by ECT and a group of 60 patients treated exclusively with antidepressants.

One of the shortcomings of the abovementioned studies is that many of them compare heterogeneous groups of patients: also, most of the figures presented concern clinically treated depressive phases. This is a disadvantage also mentioned by Angst *et al.* (*2*) and Klerman (*11*). In other words: these longitudinal studies present insufficient data on the number of, say, milder depressive phases not requiring clinical treatment. A preliminary summary of the data from the literature leads to the impression that antidepressant medication, particularly if more protracted, is more likely to be followed by an increase than by a decrease in the number of recurrence in recurrent vital depressions. In this respect a more optimistic report was recently published by Saran (*22*): 25 patients with recurrent endogenous vital depressions were followed up over a 5-year period. During the latter three years of this period the number of depressive phases was significantly smaller than during the former two years. This study thus indicated overall improvement in the course of recurrent vital depressions. Saran can give no definite explanation of this finding, but is willing to attribute the improvement in part to more systematic use of antidepressants. In a double-blind study of 93 patients, Mindham *et al.* (*19*) demonstrated that the number of recurrences was significantly smaller in patients who had received a maintenance dose of amitriptyline during a 6-month period than in a placebo group.

Reviewing these facts, we find that it remains a moot point whether the course of recurrent endogenous/vital depressions changes in response to long-term antidepres-

sant medication. It may be mentioned in passing that an evaluation of lithium prophylaxis is not within the scope of this article.

Another difficulty lies in the fact that the (endogenous) vital depression has as such a recurrent course while there are no sufficient verified data on the normal or genuine recurrent course. This has been pointed out in a Leading Article in The Lancet (*16*). It maintains that, if the number of recurrences is smaller during the therapeutic period, this does not as such warrant a conclusion in favour of a therapeutic effect, particularly if viewed against the background of the in fact unpredictable recurrent course of the condition *per se*.

Comparing patients, therefore, attempts should be made to ensure that groups compared are as homogeneous as possible, particularly in terms of age, type of psychosis or depression, and earlier phases. Invariably it proves to be very difficult to arrange groups which fulfil these criteria. Ideally, moreover, studies of the course in individual patients should compare periods in which the risk of recurrence is the same, and this is likewise a criterion which it is difficult to fulfil.

Finally, it is of essential importance to collect data on *all* the depressive phases which a patient has experienced in a given period of time. As already indicated, many of the studies in the literature fail to fulfil this criterion.

The study to be reported here was an attempt to fulfil these criteria to the best possible extent.

PERSONAL OBSERVATIONS

Method and material

All patients in whom vital depression was diagnosed and who were treated clinically or as out-patients during the years 1965, 1966 and 1967, were followed up until 31st December 1971. At least four times per year the patients were summoned for a follow-up examination, but this was often done more frequently in accordance with the course taken. Six female and four male patients withdrew from these follow-ups. Further information on these patients was obtained from their family doctors; in none of them had recurrences been noted.

Of course a number of patients were eliminated in the course of the follow-up period, either due to death or because they moved elsewhere; one man and one woman moved elsewhere; three men and six women died during the follow-up period (two women committed suicide during a depressive phase and the remaining seven patients died from non-psychiatric causes). Thus there remained two groups: 56 women and 28 men. These two groups were each divided into five age categories: < 40, 40–49, 50–59, 60–69, and 70 and over (always counting from the end of the study; see Tables 2 through 4).

In all cases, case histories were available to give information on the course of illness, if any, prior to the follow-up period. In this respect is is to be noted that the patients came from a geographically well-defined area: generally the Northern part of the

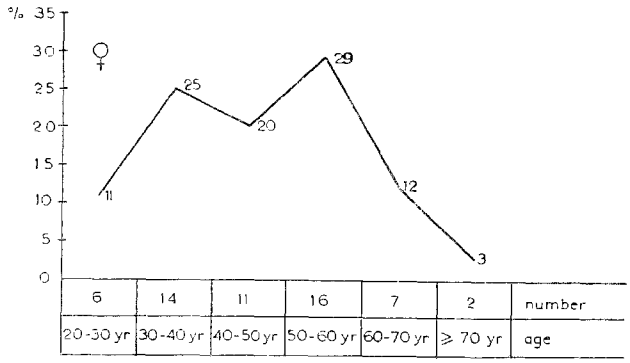

Fig. 1. Classification of the 56 female patients according to age at onset of the first depressive phase.

Isle of Walcheren, including the city of Middelburg. The age at which the *first depressive phase* occurred was established for all patients (Figs. 1 and 2).

The age distribution largely agreed with the data from the literature, *e.g.* Angst *et al.* (*1*). A general orientation on a possible familiar hereditary taint or *hereditary factors* was derived from the history of endogenous depressions and/or symptoms of manic–depressive psychoses in direct relatives: father, mother, brother(s), sister(s).

The extent to which *psychogenic factors* could have been of importance was likewise studied; the premorbid personality was given attention in this context.

The basic attitude on *therapy* was: systematic treatment with tricyclic antidepressants, combined with ECT if indicated.

Finally, an *analysis of cycle durations* was made. Efforts were made to establish whether or not a significant change in cycle durations occurred after institution of systematic treatment with tricyclic antidepressants.

Results

(1) Hereditary factors

Hereditary factors were demonstrable in 16 female and 10 male patients. The

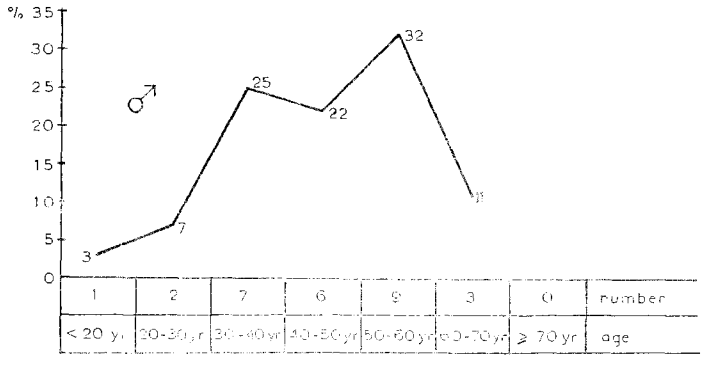

Fig. 2. Classification of the 38 male patients according to age at onset of the first depressive phase.

TABLE 1

PRESENCE AND DISTRIBUTION OF HEREDITARY FACTORS IN [illegible] FEMALE AND 10 MALE PATIENTS

Women Nos.	*7*	*12*	*13*	*14*	*17*	*18*	*23*	*32*	*34*	*37*	*[illegible]*	*39*	*44*	*45*	*52*	*54*
P	+	+	+					+								
M				+		+			+	+	+		+	+		+
F	+									+	+				+	
S			+		+		+			+		+				

(Patients 17 and 23 are sisters)

Men Nos.	*2*	*3*	*7*	*8*	*13*	*15*	*24*	*25*	*27*	*28*
P		+			+	+	+	+	+	+
M			+			+				
F	+									
S	+			+					+	

P: father; M: mother; F: brother(s); S: sister(s).

distribution of these factors (hereditary taint) over father (P), mother (M), brother(s) (F), sister(s) (S) is shown in Table 1.

(2) Significance of psychogenic factors and premorbid personality

Psychogenic factors were found to be of significance in 17 male patients. In 11 of these patients (No. 2, 10, 11, 13, 14, 15, 20, 21, 24, 25, 26) the personality structure showed features indicative of statothymia, *i.e.* the statothymic predepressive characteristics described in the introduction. Most of these psychogenic factors involved overexertion in the work situation. An interaction between what may be called the psychotraumatic situation and the statothymic state existed in all these cases. It was a conspicuous finding that in the female patients the possible influence of psychogenic factors was relatively less frequently involved (in only 9 patients). The majority of these cases entailed situational stress resulting from a change of residence, unsolvable marital conflicts, family conflicts, loss of marital partner, imminent bankruptcy, etc. It was also conspicuous that none of the female patients showed statothymic characteristics.

(3) Therapy

Therapy in all cases consisted of systematic medication with tricyclic antidepressants and, if indicated, ECT—always in accordance with the principles outlined in the introduction.

A number of patients received a maintenance dose of antidepressants throughout the period of observation (see Tables 2 through 4). If depressive phases recurred in

these cases, then the maintenance dose was increased; in a few cases (4 female and 2 male patients) it was thus possible to cope with recurrence in an out-patient setting.

This study has confirmed that ECT is often indispensable in the treatment of vital depression. This is demonstrated by the following data. Before the introduction of systematic antidepressant medication, the 56 female patients experienced a total of 35 depressive phases, in 16 of which ECT was resorted to. During the follow-up period these female patients totalled 126 depressive phases, in 23 of which ECT was combined with the antidepressant medication. The corresponding figures for the 28 male patients were: 18, with ECT in 6, and 51, with ECT in 12.

It was also established that some patients initially showed an adequate response to antidepressant medication but in subsequent recurrences proved to have become resistant to this medication. A change of drug sometimes was, but often was not effective so that ECT had to be resorted to after all. This was the case in No. 26, 44, 52 and 55 of the female, and in No. 13 and 25 of the male patients. A striking finding was that female patients 52 and 55 remained free from depression until the end of the follow-up period on a maintenance dose of chlorimipramine.

(4) Analysis of cycle durations, change of recurrent course?

Tables 2 through 4 indicate the depressive phases which occurred during the period 1940 through 1971 in all patients in the various age categories. They also indicate the cycle duration in months (cycle duration = the interval between the onset of a depressive phase and the onset of the next depressive phase, including the free interval).

For the purpose of statistical analysis, the interval in months between the onset of the last depression and the closing date of the study (31st December 1971) was established for each patient. As indicated, the question studied was whether in the patients concerned the cycle duration changed (decreased) after 1st January 1965, *i.e.* after institution of more systematic antidepressant medication.

It was found of relevance to establish the mean cycle duration per patient, thus giving a patient with frequent cycles less 'weight' than the one with few cycles, *i.e.* few recurrences. Also, a distinction must be made between patients in whom cycles occurred both before and after 1st January 1965, and those in whom cycles were demonstrable only before or only after this data. In the former case we statistically have a related sample, while in the latter case we have an independent sample. Of course this implies non-identical statistical testing.

Table 5 presents the arithmetic means, the medians of the mean cycle durations, the mean cycle duration and the median cycle duration in both total groups (in the latter, the cycle duration was not first averaged per patient).

The figures obtained warrant the conclusion that, after 1st January, both the female and the male patients showed a decrease in the arithmetic mean and in the median of the mean cycle durations. The same applies to the mean cycle duration and the median cycle duration.

Only the independent sample of the male group showed an increase; not too much value should be attached to this because observations prior to 1st January 1965

TABLE 3

FEMALE PATIENTS AGED 40 THROUGH 49 (Nos. 40 through 46) AND AGED UNDER 40 (Nos. 47 through 56); OTHERWISE AS TABLE 2

Patient No.	*Age at onset 1st phase*	*Calendar years*																
		40–50	*51*	*52*	*53*	*54*	*55*	*56*	*57*	*58*	*59*	*60*	*61*	*62*	*63*	*64*	*65*	*66*
40	43																	
41	42																	
42	36																◐	
43	39																	◐
44	36															◐		◐
45	39																	
46	37																	◐
47	34																	◐
48	35																	
49	27										◐							◐
50	32																◐	◐
51	31																◐	
52	25										◐							
53	29																	
54	28																	
55	25																	◐
56	22																◐	

concerned only a single patient. The difference between before and after 1st January 1965 was more marked in the female than in the male patients. Upon summation of the related and the independent sample, the mean of the means in the men was 49.7 prior to 1st January 1965, and 24.6 after this date; the corresponding figures for the females were 93.8 and 18.8.

It is to be noted that the abovementioned means and medians refer to cycles completed before 31st December 1971; in other words: cycles not completed by this date are not considered. Most of the latter were protracted cycles which still continued on 31st December 1971. In fact it can be stated that disregarding these uncompleted cycles shortens the mean cycle duration. The uncompleted cycles can be accounted for in two ways:

(a) on the basis of the assumption that a new depressive phase begins in each patient on 1st January 1972; this can be called a minimum estimate of the uncompleted cycle duration;

(b) on the basis of the assumption that 31st December 1971 is a random moment in the still uncompleted cycle duration; the best estimate in that case is that this moment is halfway the cycle duration; in other words: this is a doubling of the minimum estimate of the uncompleted cycle duration.

These estimates of uncompleted cycle durations are presented in Table 6, the figures referring to assumption (b) being given in brackets. Table 6 shows that, even allowing

67	68	69	70	71	Cycle duration (months)	P/K	A.D. CONT.	E.S.	HER.	PS.
◐					—	P	+			
◑					—	P	+			+
					—	P	+			
◑		◐		◐	7-32-19	K	+			
◐	◐				23-4-20	K	+	+	+	
◐					—	K	+		+	
					—	P				
	◐		◐		22-21	K	+			+
◐					—	P	+			+
					85	P	+			
	◐				8-28	K				
	◐				32	K	+			
◐◐	◐◐◐	◐◐◐	◐◐◐		96-3-6-2-4-3-2-7-5-3-2	K	+	+	+	
◐	◐		◐		11-25	K	+			
◐					—	K			+	
◐	◐	◐	◐	◐	17-10-10-9-4	K	+	+		
					—	P				

for the minimum estimate of the uncompleted cycle duration, the mean and the median of the mean cycle durations are decreased in the female patients. This also applies to the mean and the median of all cycle durations. The above continues to apply to the female patients when assumption (b) is applied.

The related sample of the male patients shows a decrease of both the mean and the median, for the uncompleted cycle duration as well as after accounting for it according to assumption (a) and assumption (b). The independent sample of the males can be disregarded (only one observation prior to 1st January 1965). Considering all cycle durations, we find an increase of the median whereas the mean decreases when assumption (a) and increases when assumption (b) is applied.

Summating the related sample and the independent sample, we find that the mean of the means in the male patients is 58.5 (60.3) before and 42.5 (76.1) after 1st January 1965, the corresponding values for the females being 93.4 (96.9) and 41.9 (77.5). The figures in brackets refer to assumption (b).

In the statistical analysis of the related samples, the Student *t*-test and the Wilcoxon symmetry test were applied. In the male patients without uncompleted cycle duration the difference between the mean cycle duration before and that after 1st January 1965 is not statistically significant ($p > 0.05$). Accounting for an uncompleted cycle duration as described above, this difference is significant ($p < 0.025$); with assumption (b), however, it is not significant ($p > 0.10$).

TABLE 4

MALE PATIENTS AGED 70 AND OVER (Nos. 1 through 3), AGED 60 THROUGH 69 (Nos. 4 through 9), AGED 50 THROUGH 59 (Nos. 10 through 19), AGED 40 THROUGH 49 (Nos. 20 through 24) AND AGED UNDER 40 (Nos. 25 through 28), OTHERWISE AS TABLE 2

Patient No	*Age at onset 1st phase*	*Calendar years*																
		40–50	*51*	*52*	*53*	*54*	*55*	*56*	*57*	*58*	*59*	*60*	*61*	*62*	*63*	*64*	*65*	*66*	*67*
1	68																		◐
2	61													◐◐	◐	◐	◐		
3	55						◐										◐		
4	63																	◐	◐
5	52																		
6	54																	◐	
7	57																◐		
8	46					◐	◐									◐		◐	
9	56																		◐
10	55																		◐
11	52																◐		
12	51																◐		
13	49																	◐	
14	52																	◐	
15	50																		◐
16	28	◐														◐			◐
17	32			◐					◐		◐		◐		◐		◐		
18	45																◐		
19	45																	◐	
20	45																		◐
21	40																		◐
22	36																◐◐		
23	35																◐	◐	
24	35																		◐
25	33																◐	◐	
26	32																◐		
27	29																	◐	
28	16				◐	◐												◐	

In the female patients without uncompleted cycle duration the difference (decrease) between the value before and that after 1st January 1965 is statistically significant ($p < 0.0025$). The difference is likewise significant ($p < 0.0005$) when assumption (a) is applied, but not ($p > 0.05$) when assumption (b) is applied.

In the analysis of the independent samples, the Mann–Whitney U-test was applied. Without accounting for the uncompleted cycle durations, the male patients were found to show an increased mean cycle duration after 1st January 1965: from 6.3 to 19.7 (Table 5). This increase is not statistically significant ($p > 0.05$). The same holds true when assumptions (a) and (b) are applied.

In the female patients without uncompleted cycle duration the mean of the mean

67	68	69	70	71	Cycle duration (months)	P/K	A.D. CONT.	E.S.	HER.	P.S.	ST.
◐					—	K			+	+	+
					6-6-7-6	P	+		+		
					120	K					
◐					10	P	+				
					—	K					
					36-19	K	+	+	+		
	◐				39	K	+				
	◐◐	◐◐	◐◐	◐	12-108-24-29-3-3-3-6-6-6	K	+	+	+	+	
◐	◐				13	P					
◐					—	P				+	+
										+	+
		◐			51	K	+				
		◐	◐		40-13	P	+		+	+	+
					31-35-18	K	+	+		+	+
					—	K		+	+		+
◐	◐				6	K		+			
◐			◐		216-36-34	K	+			+	
				◐	60-24-24-24-28-80	P	+				
					—	K				+	
	◐				22	P					
◐					—	P	+			+	+
◐				◐	49	K				+	+
					6	K		+		+	
					14	P					
◐	◐				5	K	+	+	+	+	
				◐	17-49	K	+	+	+	+	
					—	P			+	+	
					—	P					
		◐			12-144-41	K	+	+			

cycle durations per patient was 115.6 before and 18.8 after 1st January 1965 (Table 5). This difference is statistically significant according to the test used ($p < 0.05$). The same holds true when assumptions (a) and (b) are applied.

Discussion and conclusions

It is of essential importance in a long-term study of the course of recurrent vital depressions that data are available on all depressive phases, including those too mild to require clinical treatment. The available literature gives no adequate information on this point because the majority of publications are confined to clinically treated depres-

TABLE 5

ARITHMETIC MEANS AND MEDIANS OF MEAN CYCLE DURATIONS, EXPRESSED IN NUMBER OF MONTHS BEFORE AND AFTER 1ST JANUARY, 1965; P-VALUES CONCERNED

	Men		*Women*	
	before 1-1-'65	*after 1-1-'65*	*before 1-1-'65*	*after 1-1-'65*
Related sample	$N = 7$		$N = 14$	
mean of means	55.9	31.6[a]	79.8	18.9[b]
median of means	40	26.5	70.5	16.4
Independent sample	$N = 1$ and 10		$N = 9$ and 15	
mean of means	6.3	19.7[c]	115.6	18.8[d]
median of means	6.3	13.5	120	18
Total number of cycle durations	$N = 19$ and 25		$N = 35$ and 71	
mean cycle duration	44.4	21.0	80.9	15.1
median cycle duration	24	14	74	12

[a] $p > 0.05$.
[b] $p < 0.0025$.
[c] $p > 0.05$.
[d] $p < 0.05$.

TABLE 6

AS TABLE 5, BUT ACCOUNTING FOR ONCE AND TWICE (in brackets) THE MINIMUM ESTIMATE OF CYCLE DURATIONS UNCOMPLETED ON 31ST DECEMBER, 1971

	Men		*Women*	
	before 1-1-'65	*after 1-1-'65*	*before 1-1-'65*	*after 1-1-'65*
Related sample	$N = 9$		$N = 23$	
mean of means	62.4	32.8 (52.6)[a]	93.8	39.5 (71.8)[b]
median of means	48	33 (45.5)	90	27.7 (42.7)
Independent sample	$N = 1$ and 18		$N = 1$ and 32	
mean of means	23 (41)	47.3 (88.9)[c]	84 (168)	43.6 (81.6)[d]
median of means	6 (6)	40.5 (76)	84 (168)	27.7 (42.7)
Total of cycle durations	$N = 22$ and 52		$N = 36$ and 126	
mean cycle duration	50.2 (54.3)	33.6 (57.1)	81.0 (83.3)	28.1 (47.6)
median cycle duration	29.5 (29.5)	31.5 (38.5)	74 (74)	21 (25)

[a] $p < 0.025$ ($p > 0.10$).
[b] $p < 0.005$ ($p > 0.05$).
[c] $p > 0.05$ ($p > 0.05$).
[d] $p < 0.05$ ($p < 0.05$).

sions. This was one of the circumstances which prompted the present study. Another prompting factor was the impression that systematic treatment with tricyclic antidepressants was more likely to increase than to reduce the number of depressive phases in these cases.

A systematic follow-up study was made of 56 female and 28 male patients over a

period of 4–7 years, data also being available on the course of the depression prior to this follow-up period. With regard to possible aetiological factors, familial hereditary taints were found in 28% of the female and 36% of the male patients. The influence of psychogenic factors provoking depression was much more frequently demonstrable in the males (17 cases = 60%) than in the females (9 cases = 16%). In the majority of the male patients, moreover, an interaction existed between the psychological stress situation and a personality which impressed as statothymic or predepressive in the sense indicated by Tellenbach (*27*, *28*). This personality was demonstrable in 11 of the 17 abovementioned male patients. It was a conspicuous fact that this statothymic premorbid personality was not demonstrable in any of the female patients. It can therefore be tentatively concluded that pure endogenous vital depression is more common among women than among men. That there were twice as many women as men in the total group of patients is in agreement with the data in the literature on larger series of patients with vital (unipolar) depressions.

A long-term evaluation of therapy with tricyclic antidepressants seemed more important than speculations about the aetiology of the vital depressions. To begin with, it was established that exclusive antidepressant medication produced an acceptable therapeutic result in only a proportion of the depressive phases observed. In a clinical setting, the antidepressants were first given intramuscularly in rapidly increasing doses, as usuall whereupon the transition to oral medication was gradually made.

During the study period of 5–7 years, the 56 female patients totalled 126 depressive phases, in 23 of which the insufficient effect of antidepressants necessitated ECT; the latter was therefore indicated in 18% of the total number of depressive phases. The therapeutic objective was always to eliminate the vital depression as quickly as possible.

The 28 males totalled 51 depressive phases during the study period; in 13 of these phases (26%), ECT proved to be indicated alongside antidepressant medication. It was found in a number of patients (4 women and 2 men, all with frequent recurrences) that the therapeutic effect of antidepressant medication diminished in each subsequent depressive phase, so that ECT ultimately was indispensable. A change of antidepressant drug had no distinct effect on the increased resistance in the majority of these cases.

The requirements which therapy must meet in order to be efficient in an often frequently recurrent condition as vital depression, are twofold. Firstly, it should eliminate the depression as quickly as possible; secondly, it should give optimal prophylaxis against recurrences (increase the cycle duration). In this context we know that continuous administration of lithium salts seems to open good perspectives which, however, are not within the scope of this article.

Our study did reveal an alternative possibility. Sometimes (but by no means always) it was possible to deal with an incipient depressive phase in the out-patient setting, *e.g.* by increasing the maintenance dose prescribed. But it was even more evident, particularly in the female patients, that more systematic long-term antidepressant medication, with or without ECT, exerts a paradoxical effect on the recurrent character of the vital depression.

In other words: this therapeutic approach was associated with an increase in recurrence rate and a decrease in cycle duration. The literature indicates that in any case recurrent vital depressions generally tend to show an increase in the number of recurrences in the course of time. Gradually, recurrences occur more quickly; the cycle duration (the interval between the onset of the depressive phase and the onset of the next depressive phase) diminishes; the litterature suggests that the duration of each subsequent cycle is about 20% shorter than the preceding cycle.

The present study showed that, particularly in the female patients, the number of recurrences had substantially increased; in these patients the decrease in mean cycle duration was statistically significant. The interpretation of this phenomenon remains difficult. Should it be regarded as an untoward long-term side effect of treatment with tricyclic antidepressants? Do psychological factors play a role in this respect? For example, in the physician–patient relationship?

Although these questions cannot be answered, their implications do not seem very plausible because the increased recurrence rate was particularly observed in the female patients, in whom the influence of psychogenic factors was relatively less than in the males. Moreover, it was characteristic of the female patients that the typical "unmotivated" depressiveness was quite common among them. This is one of the characteristics of the endogenous vital depression and it was quite clearly indicated by the patients themselves, in retrospect.

SUMMARY

A systematic follow-up study was made, until 31st December 1971, of 56 female and 28 male patients treated for vital depressions clinically or as out-patients in the years 1965, 1966 and 1967. During the follow-up period the 56 female patients experienced a total of 126 vital depressive phases, in 23 of which (18%) ECT proved to be indicated alongside treatment with tricyclic antidepressants. The same applied to 12 (26%) of the 51 depressive phases which occurred during the follow-up period in the 28 male patients.

Psychiatric evidence of a familial hereditary taint existed in 28% of the women and 36% of the men. Probably depression-provoking psychogenic factors seemed of importance in 17 (60%) of the male patients. In 11 of these 17 patients the premorbid personality showed the features of Tellenbach's 'melancholic type' (statothymia). Psychogenic factors seemed involved in the vital depression in only 6% of the female patients.

Particularly in the long view, systematic treatment with tricyclic antidepressants proved to be associated with an increase in the total number of recurrences (*i.e.* a decreased cycle duration as compared with that prior to the follow-up period). This was found to be statistically significant in the female patients.

The question arises whether such an increased number of depressive phases whould not be regarded as a side effect or paradoxical effect which, after protracted therapy, is produced by the tricyclic antidepressants so far most commonly used.