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Stepwise regression analysis of an intensive 1-year study of delirium tremens

G. Stendig-Lindberg and N. Rudy

An intensive 1-year study was carried out on 41 male patients, mean age 49, mean hospitalization time 49 days, admitted to a special ward of the Beckomberga Hospital with the diagnosis of delirium tremens and 50 concomitant somatic and psychiatric diagnoses (1–9 per capita), and given a standardized treatment. The mean duration of delirium tremens after admission was 2 days; 76 % recovered within 48 h. The duration after admission was positively correlated to age, number of previous delirium tremens, negatively correlated to B-haemoglobin and B-haematocrit for laboratory data obtained within the first 24 h and was positively correlated to blood sugar and S-creatinine on data taken within 40 h (Pearson correlation matrix).

Stepwise multiple regression (SWR) based on 46 quantitative and dummy variables (the latter used to represent the presence of various concomitant diseases) was employed to identify the factors predicting the duration of delirium tremens. On final SWR analysis, which limited the number of observations to cases with complete observation vectors, the following regression equation was obtained: Duration after admission = 3.47–0.93 (S-magnesium)–0.29 (B-eosinophils) + 0.62 (liver disease), $P > 0.05$, $n = 14$. Although the regression coefficients were not statistically significant, S-magnesium, negatively associated with the duration after admission, offered 20 % out of the total 38 % of explanation given, whereas B-eosinophils, negatively associated, offered 12 %, and liver disease, positively associated, 6 %.

The choice by the SWR program of S-magnesium as the most important factor in predicting the duration of delirium tremens is consistent with clinical evidence that alcohol ingestion causes magnesium diuresis and that magnesium deficiency is present in chronic alcoholism. In view of this knowledge, it is reasonable to assume that the lack of statistical significance is due to the small sample size rather than to the alternative that no explanation is offered by S-magnesium. Furthermore, B-haemoglobin, S-potassium, S-ASAT, and S-ALAT, known to be characteristically altered in delirium tremens, were found on forcing (a variant of SWR) to be of secondary importance to S-magnesium as explaining factors, whereas blood sugar and S-creatinine derived part of their explaining power from S-magnesium.

In conclusion, extensive use of SWR analysis based on 46 potential explaining variables points to serum magnesium concentration as the most important factor in predicting the duration of delirium tremens.

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Key words: Delirium tremens – standardized treatment – concomitant disease – regression analysis – serum magnesium concentration.

As a part of a cross-national Scandinavian investigation, initiated by the Nordic Council and recommended by the Nordic Committee for Alcohol Research, the Swedish intensive 1-year study of delirium tremens was carried out at the Beckomberga Hospital delirium tremens ward, commencing December 1, 1962, and terminating November 30, 1963.

The study was structured according to the recommendations scheduled for the cross-national investigation. One of these was, e.g., to analyze the frequency, intensity and duration of part-symptoms of delirium tremens (e.g. hallucinations, anxiety, tremor) as indices of the severity of delirium tremens; an analysis carried out in the simultaneous Danish study (*Nielsen* (1965)).

However, the standardization of treatment, introduced shortly prior to the commencement of the study, led to further reduction of the duration of delirium tremens at the special delirium tremens ward of Beckomberga Hospital, which made the analysis of the part-symptoms no longer practicable. Consequently, the working through of the Swedish data was abandoned.

More recently, however, the finding of an association between a biochemical parameter and the onset of alcohol encephalopathy as a sequel to delirium tremens (*Stendig-Lindberg* (1974)) caused renewed interest in analyzing simultaneously the biochemical data, the incidence of concomitant disease and other relevant factors as possible determinants of duration of delirium tremens, using the source data of the Swedish intensive 1-year study.

The purpose of the present work was 1) to report the treatment methods used and the results obtained in a 1-year intensive study of delirium tremens; 2) to assess the relevance of biochemical and other relevant factors as determinants of the duration of delirium tremens by means of advanced multiple regression analysis techniques.

MATERIAL

The material consists of 41 male patients admitted consecutively during a period of 1 year to the Beckomberga Hospital under the diagnosis of delirium tremens: for age distribution, see Table 1.

Period of hospitalization

Table 2 shows that the shortest period of hospitalization was due to death on the 2nd day in acute liver necrosis and subdural haematoma (case No. 32), and to transfer on the 3rd day after recovery from delirium tremens to a somatic hospital for treatment of haematemesis (oesophageal varices), which later proved fatal (case No. 1). The longest hospitalization period was found in three patients with Korsakoff's psychosis combined with several somatic concomitant diagnoses (case Nos. 28, 40, 41).

Table 1. *Delirium tremens material*

	Age on admission (n = 41)				
Age	20–29	30–39	40–49	50–59	60–69
No. cases	1	6	11	18	5

$\bar{x}$ 49.3; s.d. 10.6; s.e.m. 1.7; range 27–69.

Table 2. *Delirium tremens material*

	Time of hospitalization						
Days	0–5	6–10	11–20	21–40	41–80	81–160	> 160
No. cases	2	1	4	21	7	3	3

$\bar{x}$ 49.5; s.d. 45.3; s.e.m. 7.1; range 2–198.

Incidence of previous delirium tremens

According to information received from the patients themselves or their medical journals, 11 out of 38 (30 %) had had delirium tremens earlier (10 patients twice and one patient four times). In three cases reliable anamnestic data could not be obtained.

Previous hospitalization

Eighteen patients at the time of onset of clinical signs of delirium tremens were hospitalized for various somatic diseases at a somatic hospital. Seventeen of the 18 patients were transferred to Beckomberga Hospital as soon as technically possible (10 within 48 h and three within 72 h) once delirium tremens was diagnosed. One patient, who had several concomitant diseases, including heart failure, was confused according to a medical note made 7 days prior to transfer. This was apparently judged as an organic confusional state, delaying transfer until the diagnosis of delirium tremens was ascertained. Consequently, none of the 18 patients received any specific treatment for delirium tremens before admission to Beckomberga Hospital.

METHODS

Diagnostic criteria

The diagnostic criteria used, followed partly those set up by *Izikowitz* (see *Allgén et al.* (1957)) and partly those of the Nordic Committee for Alcohol Research (*Nielsen* (1965)). All patients had to fulfill the following diagnostic criteria: the presence of disorientation to all qualities, hallucinations, severe motoric restlessness, severe anxiety together with the classical symptom-triad of predelirium: tachycardia, tremor and perspiration. Three independent observers were involved in the diagnostic evaluation of the patient: a) the doctor who referred the patient to the hospital, b) the doctor on emergency duty who examined the patient on admission and c) the doctor who received him in the

ward (in the majority of cases, by S.-L.). The head of the department (*Beander, G.*) was responsible for the final decision as to whether all the diagnostic criteria had been fulfilled in each case.

Delirium tremens was considered terminated when the patient was free from the signs and symptoms, although some degree of coarse finger tremor may have persisted.

Assessment of the duration of delirium tremens

Total duration of delirium tremens. This is defined as 1) the duration from the onset of delirium tremens until admission plus 2) the duration of delirium tremens after admission.

Duration prior to admission. When calculating the duration of delirium tremens prior to admission, in cases commencing at home, a degree of accuracy of 8–12 h was arrived at. Information such as "several hours" or information stating that "the patient became ill on the day of admission" was interpreted as a duration of 8 h. Information such as "last night" or "half a day before admission" was interpreted as a duration of 12 h.

The duration for the 18 cases in which delirium tremens commenced at a somatic hospital, was recorded with an average accuracy of 12 h (since only the date and not the exact hour of onset was recorded in the medical referral or journal).

Duration of delirium tremens after admission. Assessment of the duration of delirium tremens was made daily during the morning round so the average duration value tended to be 12 h too high.

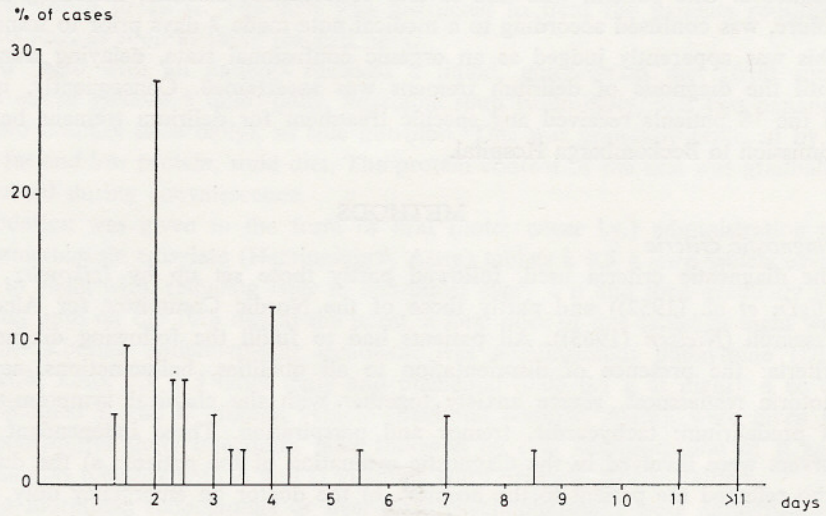

Fig. 1. *Total duration of delirium tremens.*

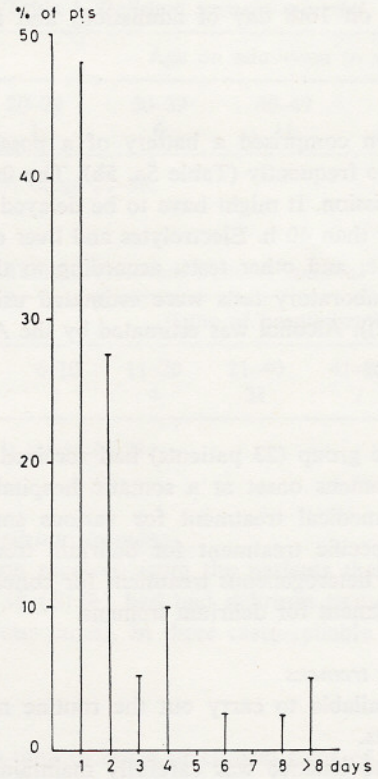

Fig. 2. *Duration of delirium tremens after admission.*

Concerning the first 24 h (day I), the intensive vigilance kept and the continuous recording of the patient's status by the staff, gave an average error of a few hours only.

Two cases (Nos. 24 and 40) were difficult to assess. Case No. 24 had concomitant diagnoses of subdural haematoma, Wernicke's encephalopathy, and abusus alia and was transferred to an acute general hospital for treatment where he died, with the terminal diagnosis of bronchopneumonia and pulmonary oedema, 21 days after admission to the Beckomberga Hospital. Case No. 40 had liver coma, ascites, subileus, a period of anuria, active lung tuberculosis, chronic emphysema and Korsakoff's psychosis and was transferred after 80 days to a sanatorium for treatment of the pulmonary disease. In the latter case, the presence of an alcohol encephalopathy and grave somatic disease made it difficult to delimit when the delirium tremens terminated. For preliminary description these two cases are marked as duration of > 11 (Fig. 1) or > 8 (Fig. 2).

Medical investigation

Investigation of the patients consisted of a thorough screening for the pres-

ence of concomitant disease, ECG screening in 33 cases (32 cases within 1 week and in one case on 16th day of admission) and laboratory screening in all patients.

Laboratory screening

Laboratory investigation comprised a battery of a possible 44 tests, however, only 35 were used more frequently (Table 5a, 5b). The first laboratory examination was made on admission. It might have to be delayed (if the patient was too restless), but not longer than 40 h. Electrolytes and liver enzymes were estimated repeatedly, as a routine, and other tests, according to the requirements of the clinical findings. The laboratory tests were estimated using methods previously described (*Salum* (1972)). Alcohol was estimated by the ADH method (*Bonnichsen & Theorell* (1951)).

Treatment

Prior to admission, one group (23 patients) had received no treatment, whereas those with delirium tremens onset at a somatic hospital (18 patients) had received heterogeneous medical treatment for various somatic diseases, but no i.v. infusion or any specific treatment for delirium tremens. After admission, all patients received 1) heterogeneous treatment for concomitant disease, 2) specific homogeneous treatment for delirium tremens.

Treatment for delirium tremens

Adequate staff was available to carry out the routine nursing techniques used for unconscious patients.

Water and electrolyte balance was carefully maintained (in dehydration the fluid intake was kept within 3 l/24 h and in anuria limited to 800 ml above the urinary output volume). Laboratory pathology was corrected as far as possible.

The rooms where the patients were nursed had cooling systems and could be cooled down to 12°C. The staff was instructed to treat the patients routinely by cooling, as soon as fever reached 38°C.

To begin with all patients received a liquid, glucose-rich diet (fruit soup with added glucose 3 times daily, vegetable soup twice daily, and two bananas or two oranges once daily), as sole nutrition. This was gradually replaced by a low fat and low protein, solid diet. The protein content of the diet was gradually increased during convalescence.

Sedation was given in the form of oral (note: never i.v.) administration of chlormethiazole edisylate (Heminevrin®, Astra) tablets à 0.5 g (two tablets every 4 h to begin with, reducing later to one tablet every 4 h and then gradually reducing until on the 10th day at the latest, a final dose of one tablet at night was given). Routine anticonvulsant treatment was administered: phenytoine (Difhydan®, Leo), 0.1 g 3 times daily and phenemal (0.05–0.1 g at night). 4 cc of a combined B and C vitamin vehicle (Bevitotal comp.®, Astra), were given in 10 consecutive daily injections, later followed by oral administration of B and C vitamins together with A and D vitamins and Litrison®, Roche, tablets.

No morphine, scopolamine or liver-toxic psychopharmaca were administered.

Table 3. *Concomitant diseases, mortality*
(key to Figs. 3 and 4)

ECG pathology with no clinical signs of heart disease (E)
Pulmonary disease (P)
CNS disease (CNS) including Wernicke's encephalopathy (CNWS in Fig. 4)
Peripheral nerve disease (PN)
GIT disease (G)
Cardiac disease (C)
Liver disease (L)
Skeletal disease (S)
Kidney disease (K)
Endocrine disease (END)
Ear, nose and throat disease (ENT)
Fractures (FR)
Other disease (0 in Fig. 3 = Carcinoma (Ca), Frost bite (FB), Bed score (BS) in Fig. 4)
Korsakoff's psychosis (Ko)
Schizophrenia (Sch)
Narcomania (N)
Mortality (M)

Table 4. *Variables used in the stepwise regression programme (SWR)*
Non-laboratory quantitative variables

No.	Variable	$\bar{x}$	s.d.	*n*
33	Age	48.8	10.5	39
34	No. of previous delirium tremens	1.4	0.6	36
44	Days of prior hospitalization in a somatic hospital	1.7	1.6	39
45	Duration before admission	1.2	1.2	39
46	Duration after admission	2.0	1.5	39

Chlordiazepoxide (Librium®, Roche) was used, 30–60 mg daily, if needed, after the termination of Heminevrin treatment.

Statistical methods

Variables

Variables used in this study are listed in Tables 4, 5a, b, and 6. The latter Table consists of the dummy variables used to represent the presence or absence of concomitant disease (see Appendix).

Laboratory variables with fewer than 10 observations were excluded. Although the laboratory data were recorded over a period of at least 10 days, only the values obtained either within 24 h, or 40 h following admission were used for data treatment. Two sets of data cards were prepared: sample A containing the laboratory findings of the first 24 h, and sample B which, in addition to sample A values, contained results of laboratory tests sampled first within 40 h of admission.

Table 5a. *Variables used in the stepwise regression programme (SWR)*
Laboratory variables

No.	Variable	$\bar{x}$	s.d.	*n*	Range of patient's values	Laboratory's range of normal values	Cases with deviant values No	%
1	B-haemoglobin (g/l)	136.7	16.3	34	106–166	136–172 (♂)	> 0	> 0
							<24	<71
2	B-leucocytes part. conc. (10^9/l)	7.15	2.98	34	3.4–14.7	3.0–7.4	> 4	>12
							< 0	< 0
3	B-polymorphonuclear leucocytes (%)	68.0	11.0	30	41–89	45–70	>12	>40
							< 0	< 0
4	B-mononuclear leucocytes (%)	2.0	2.4	30	0–9	2–5	> 2	> 7
							<17	<57
7	B-lymphocytes (%)	24.8	10.0	30	9–45	20–45	> 0	> 0
							< 9	<30
8	B-monocytes (%)	4.1	3.8	30	0–14	4–8	> 3	>10
							<16	<53
9	B-haematocrit (vol. %)	41.8	5.6	32	30–52	42–50	> 1	> 3
							<21	<66
10	E-sedimentation rate (mm/h)	23.1	26.0	34	2–112	<12 (♂)	>18	>53
							< 0	< 0
11	Prothrombine index	95.7	12.2	29	62–114	80–120	> 0	> 0
							< 3	<10
12	S-diastase (U/cc)	1.6	1.0	24	0.5–4.2	<2.3	> 7	>29
							< 0	< 0
13	Blood sugar (mmol/l)	5.19	2.17	34	2.8–15.8	3.3–5.6	>10	>20
							< 3	< 9
14	Blood alcohol* (ADH method) (mmol/l)	0.08	0.04	7	0.01–0.11	0	7*	>25
15	B-non-protein nitrogen (mmol/l)	23.93	6.54	11	15.0–35.0	<21.5	> 7	>67
							< 0	< 0
16	S-creatinine (μmol/l)	114.0	72.2	20	61.9–327.1	<131	> 4	>20
							< 0	< 0
17	Standard bicarbonate (mmol/l)	22.65	3.40	34	15.0–30.0	18.9–24.5	> 7	>21
							< 3	< 9
18	S-potassium (mmol/l)	4.20	1.12	37	2.8–9.3	3.6–5.1	> 5	>14
							<11	<30
19	S-sodium (mmol/l)	140.9	6.63	37	128–163	137–148	> 4	>11
							< 9	<24
20	S-chlorides (mmol/l)	100.1	4.9	34	92–210	95–107	> 2	>59
							<10	<29
21	S-magnesium (mmol/l)	0.814	0.178	18	0.53–1.26	0.75–0.95	> 3	>17
							< 8	<44
22	S-bilirubin (μmol/l)	15.78	11.59	30	1.71–63.3	<17	> 6	>20
							< 0	< 0
23	Thymol (U)	0.7	0.3	28	0.03–1.5	<4	> 0	> 0
							< 0	< 0
24	S-ASAT (U/cc)	131.0	158.2	37	16–760	<40	>32	>86
							< 0	< 0
25	S-ALAT (U/cc)	74.9	67.7	36	23–380	<35	>34	>94
							< 0	< 0
26	S-ICD (U/cc)**	528.2	685.8	23	69–3170	<150	>13	>56
							< 0	< 0

* Seven of 28 patients, i.e. one in four has alcohol in blood.
** S-LD, not included in the statistical analysis, was raised in 6/8 cases (75 %).

Table 5b. *Variables used in the stepwise regression programme (SWR)*
Laboratory variables with limited variability

No.	Variable	*n*	Cases with deviant values No.	%
5	B-eosinophils	32	16 patients have 0 16 patients have 1–4	50
6	B-basophils	32	0	0
27	U-sugar	35	9	26
28	Ketone bodies	28	2	7
29	U-diastase	31	1	3
30	U-urobilin	33	28	85
31	U-urobilinogen	33	27	82
32	U-albumin	35	11	31

Table 6. *Variables used in the stepwise regression programme (SWR)*
Dummy variables for concomitant diseases

No.	Variable	*n*	Cases affected No.	%
35	Kidney disease	39	3	8
36	Liver disease	39	7	18
37	Pulmonary disease	39	12	31
38	Cardiac disease	39	8	21
39	CNS disease	39	9	23
40	ECG pathology without clin. signs of cardiac dis.	32	13	41
41	GIT disease	39	9	23
42	Endocrine disease	39	3	8
43	Narcomania	39	3	8

Multiple regression

In order to relate the duration of delirium to the recorded variables, a variant of multiple regression, called stepwise regression (SWR), was employed (see Appendix). The general form of the relationship was taken to be: duration of delirium tremens = f (laboratory variables, non-laboratory quantitative variables, concomitant disease dummy variables).

Of the two forms of duration of delirium tremens recorded, the duration after admission to Beckomberga Hospital was chosen as the dependent variable. This was done because of the absence of correlation between duration prior to admission and duration after admission, and because no treatment for delirium tremens was given prior to admission, whereas a standardized treatment for delirium tremens was given to all patients after admission.

a) *Correlation matrix.* The starting point of stepwise regression is a matrix of correlation coefficients for each pair of variables. Since not all variables were available for each patient (i.e., the vectors of observations were sometimes in-

complete) the correlation matrix was calculated using all available pairs of observations within the patient vector in samples A and B.

b) *Stepwise Regression Program* (SWR). The correlation matrix based on incomplete observation vectors, is not ideal as a basis for the final SWR, because each correlation coefficient in the matrix may be calculated from a different group of patients.

However, it was a useful tool for an initial SWR screening, which provided a list of factors which were then reviewed in the light of substantive knowledge. The reviewed results then served as a basis to define a final model to be submitted to standard SWR for which only complete observation vectors were used.

For the initial run, the correlation matrix for sample B of the source data ($n = 41$) was submitted to the SWR, in order to obtain maximum possible information.

Before presenting the model to the final SWR, we removed case Nos. 24 and 40 (for which a precise assessment of the duration of delirium tremens after admission could not be made) and considered only the remaining 39 patients (Tables 4, 5a, b, 6). The SWR was left free to select variables to be added to the model at each step (see Appendix).

c) *Forcing*. For this variant of SWR (see Appendix) the variables were selected from the results of the correlation matrix and SWR results.

RESULTS

Total duration of delirium tremens

The total duration of delirium tremens was: mean 3.2, s.d. 2.1, s.e.m. 0.34, $n = 39$, range 1.5–11. The shortest duration was 17 h. The distribution is given in Fig. 1.

Duration of delirium tremens after admission

The duration after admission was 1 day for 49 % of the patients and 2 days for 27 % of the patients. Together 76 % of the patients recovered within 48 h. The mean duration was 2.0, s.d. 1.54, s.e.m. 0.25, $n = 39$, range 1–8. The distribution is given in Fig. 2.

The longest duration of delirium tremens of 8 or > 8 days (case Nos. 24, 28 and 40) coincided with the presence of an alcohol encephalopathy (*Stendig-Lindberg* (1974)), Fig. 4, Table 3.

Concomitant disease

Fifty concomitant diagnostic entities, were found in this material (46 somatic and four psychiatric). Table 3 and Fig. 3 illustrate the percentage distribution of concomitant pathology.

Each concomitant diagnosis occurred with the frequency of between one case (i.e., frostbite and Pick's restrictive pericarditis) and 14 cases (pathological ECG in the absence of clinical signs of cardiac disease) Table 3, Figs. 3, 4.

Forty patients had concomitant somatic diagnoses, the only patient who did

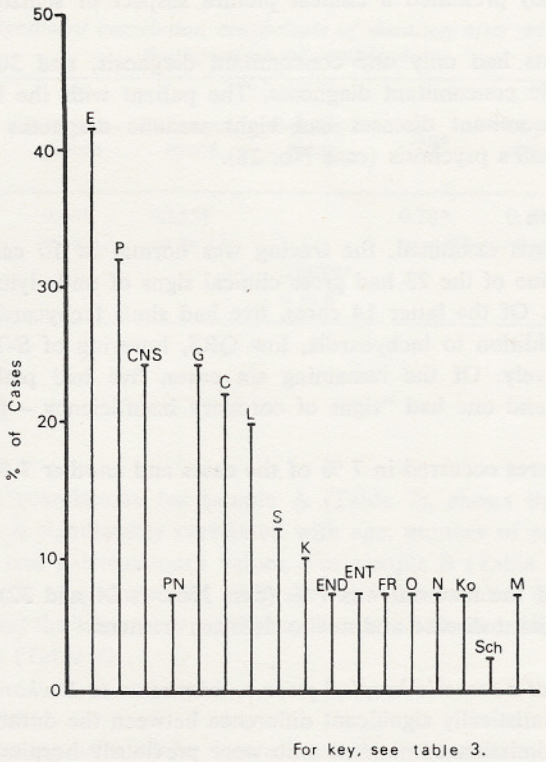

Fig. 3. *Concomitant disease and mortality in delirium tremens.*

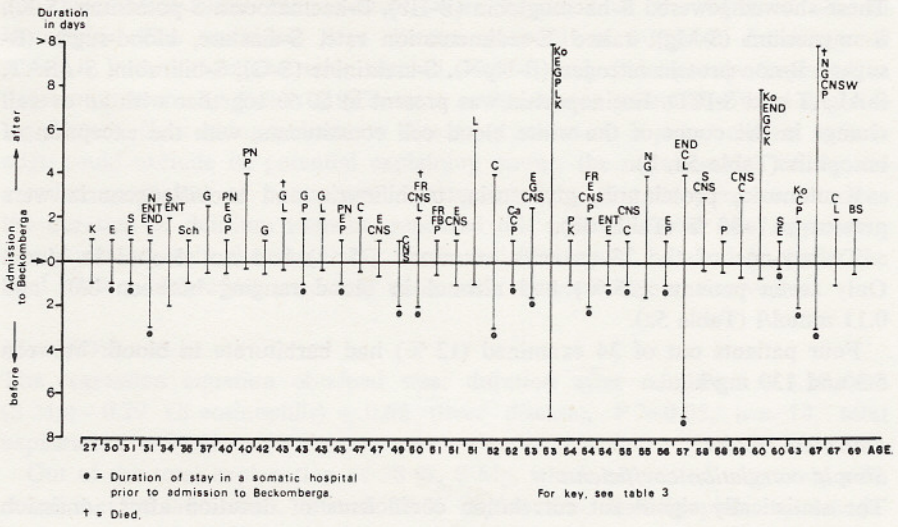

Fig. 4. *Duration of delirium tremens related to age and concomitant disease.*

not (case No. 35) presented a clinical picture suspect of schizophrenia (Table 3, Fig. 4).

Eleven patients had only one concomitant diagnosis, and 30, between two and nine somatic concomitant diagnoses. The patient with the highest number of somatic concomitant diseases had eight somatic diagnoses and one psychiatric: Korsakoff's psychosis (case No. 28).

ECG examination

Of the 33 patients examined, the tracing was normal in 10 cases and pathological in 23. Nine of the 23 had gross clinical signs of underlying heart disease and 14 had not. Of the latter 14 cases, five had sinus tachycardia and another three had, in addition to tachycardia, low QRS, lowering of S-T segment, and low T, respectively. Of the remaining six cases, five had pathological ST-T and/or T wave and one had "signs of coronary insufficiency – possibly vegetative".

Epileptic seizures occurred in 7 % of the cases and another 7 % had a history of seizures.

Mortality

The mortality of the material was 7 % (case Nos. 1, 24 and 32), due to severe somatic concomitant disease and not to delirium tremens.

Hospitalization at a somatic hospital prior to admission to Beckomberga Hospital

There was no statistically significant difference between the duration of delirium tremens after admission of patients who were previously hospitalized and those who were not. The patients previously hospitalized are indicated on Fig. 4.

Laboratory results

These showed lowered B-haemoglobin (B-Hb), B-haematocrit, S-potassium (S-K), S-magnesium (S-Mg), raised E-sedimentation rate, S-diastase, blood-sugar (B-sugar), B-non-protein nitrogen (B-NpN), S-creatinine (S-G), S-bilirubin, S-ASAT, S-ALAT and S-ICD. Eosinopoenia was present in 50 % together with an overall change in the count of the white blood cell constituents, with the exception of basophils (Table 5a, b).

Kentonuria, proteinuria, glycosuria, urobilinuria and urobilinogenuria were present in 7–85 % (Table 5b).

Twenty-one of the 28 patients examined (75 %) had no alcohol in blood. Only seven patients (25 %) had alcohol in blood ranging between 0.01 and 0.11 mmol/l (Table 5a).

Four patients out of 34 examined (12 %) had barbiturate in blood: between 5.3 and 130 mg/l.

Statistical results

Simple correlation coefficients

The statistically significant correlation coefficients of duration after admission and S-Mg are presented in Tables 7 and 8.

Table 7. *Significant correlation coefficients of duration after admission and S-magnesium of sample A*

	B-haemo-globin	B-haema-tocrit	S-potas-sium	Age	No. previ-ous d.t.	Another hospital prior to admission
Duration after admission	–0.64* $n = 12$	–0.55* $n = 11$		0.28* $n = 39$	0.39** $n = 36$	
S-magnesium			0.90*** $n = 8$			–0.61* $n = 8$

* $= P > 0.05$.
** $= P > 0.01$.
*** $= P > 0.001$.

The table of correlations for sample A (Table 7), shows that the duration after admission is significantly correlated with age, number of previous delirium tremens, B-Hb and B-haematocrit values. For sample B (Table 8), the duration after admission is also associated with age, and the number of previous delirium tremens and the laboratory variables: B-sugar, S-Cr and the B-mononuclear leucocyte count (Table 8).

Initial SWR results

The initial screening selected in decreasing order of importance the following variables: B-eosinophils, S-Mg, pulmonary disease and liver disease.

The first three variables associated negatively with duration after admission and the last, positively. These results of the initial screening, using sample B and incomplete observation vectors, were reviewed in the light of clinical knowledge. The variables: liver disease, as well as S-Mg (a deficiency of which is known to characterize alcohol disease) and eosinopoenia (reported in delirium tremens by *Salum* (1972) were acceptable as potentially valid explaining factors. Concerning pulmonary disease, whereas no *a priori* clinical knowledge could exclude its potential explaining power, the negative sign of the regression coefficient of pulmonary disease, implying that its presence shortens the duration of delirium tremens, rendered this result illogical (see Appendix). Consequently, only the remaining three variables could be used to build the final SWR model, which used only cases with complete observation vectors.

Final SWR results

The regression equation obtained was: duration after admission = 3.47–0.93 (S-Mg) – 0.29 (B-eosinophils) + 0.62 (liver disease), $P > 0.05$, $n = 14$, total explanation = 38 %.

Out of the total explanation of 38 %, S-Mg, which associated negatively with duration after admission, offered 20 % explanation, B-eosinophils, also negatively associated, 12 % explanation and liver disease, positively associated, 6 % explanation.

Table 8. *Significant correlation coefficients of duration after admission and S-magnesium of sample B*

	B-haemo-globin	B-mono-nuclear leucocytes	B-sugar	B-alcohol	S-cre-atinine	S-ALAT	U-albumin	Age	No. previ-ous d.t.
Duration after admission		–0.39* $n = 30$	0.35* $n = 34$		0.51** $n = 20$			0.28* $n = 39$	0.39** $n = 36$
S-magnesium	–0.41* $n = 17$			0.74* $n = 9$		0.53* $n = 18$	0.54* $n = 10$	–0.40* $n = 18$	

* $= P > 0.05$.
** $= P > 0.01$.
*** $= P > 0.001$.

Table 9. *Results of forcing in pairs*

	Variable	Forced first	Left free	*n*
A	S-potassium	0	6	17
	S-magnesium	15	20	
B	B-haemoglobin	1	1	33
	S-potassium	13*	13*	
C	B-haemoglobin	4	too small to compute	17
	S-magnesium	21	17	
D	B-haemoglobin	0	1	32
	S-ALAT	5	5	
E	Blood sugar	30*	21	15
	S-Magnesium	20	11	
F	S-creatinine	0	0	8
	Blood sugar	81**	83**	
G	S-creatinine	39	50*	10
	S-magnesium	13	24	
H	S-ASAT	0	1	18
	S-magnesium	14	15	
I	S-ALAT	2	0	17
	S-magnesium	14	12	

* $= P < 0.05$.
** $= P < 0.01$.

Forcing

The results of forcing in pairs of other potentially explaining laboratory variables are presented in Table 9.

On forcing S-K first, leaving S-Mg free, S-K offers no explanation of the duration of delirium tremens. The small explanation acquired by S-K on forcing S-Mg first, is due to its association with S-Mg (Table 9: A).

When B-Hb is forced first, with S-K, S-Mg or S-ALAT left free, it offers virtually no explanation (Table 9: B, C, D) indicating that the statistically significant correlation coefficient between B-Hb and the duration, found on the correlation matrix (Table 7), is due to the association of B-Hb with a number of other laboratory variables, e.g. S-Mg.

B-sugar shows on forcing that a good part of the explanation attributed to B-sugar (Table 8) derives from its association with S-Mg (Table 9: E).

S-Cr, when forced first with B-sugar left free, offers no explanation (Table 9: F). When forced first with S-Mg left free it offers 39 % of explanation ($P < 0.05$) (Table 9: G) which suggests that S-Cr and S-Mg enhance the explaining power of each other.

Neither S-ASAT nor S-ALAT when forced or left free, offer any appreciable explanation (Table 9: H, I).

DISCUSSION

Age distribution

The age distribution of the present material does not differ statistically from

that of the material of *Nielsen* (1965), or that of *Salum* (1972), a study originating from the same special delirium tremens ward of the Beckomberga Hospital, and completed barely a year before commencement of the present study.

Duration after admission

The duration after admission differs significantly from the durations reported by *Nielsen* (1965) ($P < 0.01$; χ^2 test) and *Salum* (1972) ($P < 0.05$; χ^2 test).

The latter durations appear to be equivalent in definition to the duration after admission as defined here, since the possible duration prior to admission to a psychiatric hospital is not specified in the two Scandinavian studies.

The shorter duration found in the present material might be due to the standardized treatment used, particularly the exclusive use of chlormethiazole edisylate (Heminevrin) for sedation and the routine early cooling of the room on rise of temperature. Some elements of the treatment, however, were similar to those used earlier by *Salum* (1972), e.g. diet and nursing routine.

Concomitant disease, incidence of epileptic seizures, mortality

The incidence of concomitant disease in this material was significantly higher than in the other two studies ($P < 0.001$; χ^2 test), apparently due both to a higher morbidity of the studied patients and the emphasis placed on somatic diagnostic screening.

The incidence of epileptic seizures was lower, although not statistically significant in comparison with *Nielsen* (1965), but statistically significant in comparison with *Salum* (1972) ($P < 0.05$; χ^2 test), probably owing to the routine use of anticonvulsant therapy as well as the routine early cooling when fever rose. *Cutshall* (1965) associated the occurrence of high fever with higher incidence of seizures in delirium tremens.

There was no statistical difference between the mortality in this material and that of the other two Scandinavian studies.

ECG pathology

ECG showed pathological changes in 70 %, compared with only 22 % in the material of *Nielsen* (1965) ($P < 0.001$; χ^2 test). The reason for this difference is not clear. It is of great interest that in 14/33 cases (42 %) there were no gross clinical signs of cardiac disease. Tachycardia was described in experimentally induced magnesium deficiency in rats, dogs and pigs and in magnesium depletion in alcoholics, whereas depressed S-T segment and T-wave abnormalities, among other ECG changes found in the 14 cases, were reported in animals and chronic alcoholics with moderately severe or advanced magnesium depletion with, or without hypokalaemia or hypocalcaemia (*Seelig* (1969)).

Laboratory results

The overall laboratory picture is consistent with that reported by *Nielsen* (1965) and *Salum* (1972). The incidence of raised S-ALAT however, was unusually high (96 %) and higher than that of S-ASAT (86 %), whilst the opposite relation prevailed in the studies of *Nielsen* (1965) and *Salum* (1972). Because of

the different laboratory methods used by *Nielsen* (1965) and, e.g. the breakdown of laboratory results into diagnostic subgroups ($D_{1,2,3}$) in the study of *Salum* (1972), a statistical comparison of the laboratory data has not been made.

Since raised S-ALAT indicates liver damage, the present material appears to show an unusually high liver morbidity. This, together with the rise in S-LD and S-ICD (75 % and 56 %, respectively) as well as S-ASAT, indicates the presence of high incidence of severe delirium tremens (*Nielsen* (1965), *Salum* (1975)). It can hardly be ascribed to a drug effect, since treatment with chlormethiazole edisylate (Heminevrin), the sedative medication used exclusively, tends to give least rise of S-ASAT and S-ALAT (*Salum* (1972)).

Salum (1972) found that raised B-NpN was most frequent in cases with severest delirium tremens (group D_3); 46 % (21 % only, in the less severe forms; $D_{1,2}$). The high incidence found in the present study (58 %), speaks, also, for the presence of a high incidence of severe delirium tremens in the present material. Similarly, the incidence of raised S-Cr (20 %) was somewhat higher than in the material of *Nielsen* (1965) (5 %). It was remarkable that in one case (No. 20), a steady rise in S-Cr continued after the termination of delirium tremens with anuria as a sequel, reaching on the 8th day, the exceptionally high value of 1944.8 μmol/l, yet recovery followed.

Alcohol in the blood was zero in 75 % of this material, which is in agreement with the findings of *Salum* (1972) (80 %) and *Nielsen* (1965) (84 %).

Statistical analysis

Correlation results

It is important to bear in mind that the correlation coefficients involving laboratory variables may be affected by the time which elapsed before the blood samples were obtained. For example, a correlation coefficient of S-Mg and S-K of sample A (Table 7) is significant at 0.1 % level ($P < 0.001$), whereas in sample B (Table 8), there is no longer a significant correlation between the two variables. Here, the change might be due to the effect of the diet which included potassium-rich fruit juices in liberal amounts. Similarly, the B-Hb values of sample A (Table 7) associate negatively with the duration of delirium tremens after admission ($P < 0.05$), while in sample B (Table 8), there is no significant correlation.

SWR results

Although no statistically significant regression coefficients on SWR with complete observation vectors were obtained, the variable first selected by the final SWR as the variable with the highest explaining power is serum magnesium concentration. The negative association found by us, i.e. the lower the serum magnesium concentration the longer the duration of delirium tremens, is supported by the following substantive knowledge: 1) alcohol ingestion is accompanied by magnesium diuresis (*Kalbfleisch et al.* (1963), *Lindenman* (1969)), 2) magnesium depletion is known to occur in chronic alcoholism. The average deficit in chronic alcoholism is 0.5 mmol/kg (*Flink* (1980)), 3) delirium tremens is a sequel of prolonged alcohol abuse. This clinical evidence supports the

view that the statistically non-significant result for S-Mg is due to the small sample size rather than to the alternative that no explanation is offered by serum magnesium concentration.

Forcing

The fact that S-K offers no explanation of its own is of importance in the light of the findings both in the experimental animal (*Whang et al.* (1967)) and in *homo* (*Shils* (1969)), which suggest that hypokalaemia may be a result of hypomagnesaemia. Furthermore, the administration of potassium infusion to delirium tremens patients with hypokalaemia has no effect on S-K (*Wadstein & Skude* (1978)). The experimental evidence of *Whang et al.* (1967), as well as the results of magnesium infusion in congestive heart failure in man (*Dyckner & Wester* (1979)) suggest that magnesium is essential for maintaining and restoring intracellular potassium.

B-Hb, known to be characteristically lowered in delirium tremens, shows on forcing to be secondary in importance to S-Mg, as an explaining factor.

The interpretation of the positive association of B-sugar and the duration of delirium tremens shown by the correlation matrix (Table 8) must be made with caution, partly because the results of forcing show that B-sugar derives part of its explaining power from S-Mg, and partly because of the glucose contained in the routine diet.

Our correlation results show, however, that B-sugar is more significantly correlated to the duration prior to admission ($r = 0.60^{***}$, $n = 34$) than to that after admission (Table 8), which means that the hyperglycaemia was already present prior to admission to the Beckomberga Hospital and receipt of the diet. This is consistent with the findings of *Allgén et al.* (1957), *Nielsen* (1965) and *Salum* (1972) who reported high B-sugar (and often glycosuria) in early delirium tremens, followed by a subsequent fall. *Cutshall* (1965) attributes the hyperglycaemia to an initial stimulation of adrenal medulla and cortex followed by impaired adrenal response with tendency to hypoglycaemia.

The positive association of S-Cr and duration in the correlation matrix (Table 8) is shown on forcing to be due to its association with S-Mg.

Salum (1972) reported that peak S-ASAT values were reached when the delirious state reached its peak intensity. *Nielsen* (1965) found a positive correlation between the severity and duration of delirium tremens' part symptoms (e.g. disorientation, convulsions) and the presence of lowered S-Mg as well as elevated S-ASAT activity. We find, however, on forcing that S-ASAT, whether forced first or second, offers virtually no explanation regarding the duration of delirium tremens, compared with that offered by S-Mg.

The finding on forcing that S-ALAT is secondary in importance to S-Mg is of interest in the light of experimental findings. In the experimental animal, magnesium supplementation (especially magnesium orotate) was found to protect the experimental animal from developing hepatic lesions induced by ethanol treatment, or CCL_4, and to mitigate the hepato-toxic effects of these agents (*Szelényi* (1973)).

Alcohol metabolism, chronic alcoholism and magnesium depletion

The metabolism of alcohol (*Hultman* (1974), *Rydberg* (1974), *Lieber* (1975), *Lundquist* (1975), *Mendelson & Mello* (1976)) affects carbohydrate, fat, protein and hormone metabolism.

Magnesium cation is required among others as co-factor in protein and nucleic acid synthesis, and in intermediary metabolism it is necessary for the storage of catecholamines in the adrenal medulla and the release of adrenaline, and for the energy processes.

One of the major reasons for magnesium depletion in chronic alcoholism is the enhanced renal excretion of magnesium (*Kalbfleisch et al.* (1963), *Lindenman* (1969)), as a direct response to alcohol ingestion. Vomiting, diarrhoea, hyperhiderosis and malnutrition may also contribute to the total magnesium loss in chronic alcoholism.

Not only is the serum magnesium concentration lowered in chronic alcoholism, as reported by *Flink* (1954) and others, but also the muscle magnesium content (*Jones et al.* (1969), *Stendig-Lindberg et al.* (1977)). The CSF magnesium is lowered in alcohol withdrawal and further significantly lowered in the presence of epileptic seizures (*Meyer & Urban* (1977)).

Neuromuscular excitability in early withdrawal, expressed as sensitivity to photic stimulation, is positively associated with degree of concomitant hypomagnesaemia and respiratory alkalosis (*Wolf & Victor* (1969)).

Belknap et al. (1978), wishing to establish whether there is brain magnesium deficiency as result of chronic ethanol intoxication, found in exposed mice that there was lower whole brain magnesium than in controls. The symptoms of alcohol withdrawal were strikingly similar to those seen in magnesium-deficient mice exposed to low magnesium diet – and no alcohol – suggesting that the magnesium deficit caused by ethanol, could contribute to the alcohol withdrawal syndrome.

Causal relation between magnesium depletion and the development of delirium tremens was first suggested by *Flink et al.* (1954), who also advocated magnesium supplementation, and *Suter & Klingman* (1955). The hypothesis was doubted, however, by *Vallee et al.* (1960) and not confirmed by the studies of *Allgén et al.* (1957) and *Salum* (1972). Nevertheless, hypomagnesaemia was most frequent in the severest form of delirium tremens (D_3) in the study of *Salum* (1972). Also *Nielsen* (1965) found correlation between low magnesium and the duration and severity of delirium tremens.

Stendig-Lindberg (1974) suggested that hypomagnesaemia could be interpreted as an indicator of a basic metabolic lesion, common to all the clinical manifestations of alcohol disease, differing merely in the extent of its severity.

Since the pharmacological action of ethanol is rather unspecific, it is desirable to locate a cellular lesion which is also found with other drugs giving rise to tolerance and dependence. If such a lesion could be demonstrated, it might explain a number of pathological processes as being secondary results of the primary biochemical lesion (*Lundquist* (1975)).

Alcohol was reported to inhibit active transport of K^+ and to inhibit the magnesium dependent Na^+–K^+-stimulated ATPase activity. The reverse was found

in rat brain homogenates following chronic administration of ethanol in dosage known to produce acquired behavioural tolerance, apparently as a compensatory phenomenon. In human erythrocytes of alcoholics, the Na^+–K^+-stimulated ATP-ase activity increased by 76 % (*Israel et al.* 1970).

Whang et al. (1974) suggested that the specific biochemical lesion of delirium tremens might be the failure of the magnesium-dependent, cell membrane Na^+–K^+ pump, which might be restored by magnesium repletion. *Hosein et al.* (1977) attempting to identify the probable mechanism of ethanol action on the membrane, using liver mitochondria of male Sprague-Dawley rats following chronic ethanol feeding, found structural derangement of the mitochondrial membrane, or enzyme microenvironment, and not merely a specific effect on the Mg^{++}-stimulated ATPase activity. Mitochondria have high magnesium concentration (*Thiers & Vallee* (1957)), higher than the cytosol (*Reed & Lardy* (1973)). Should ethanol prove to disrupt the integrity of mitochondrial membrane, efflux of magnesium would follow, offering one explanation for the magnesium diuresis accompanying ethanol ingestion.

CONCLUSION

SWR selects serum magnesium concentration as the first variable of importance in explaining the duration of delirium tremens. Furthermore, the results of forcing show that the changes in the level of e.g. B-haemoglobin, S-potassium and in S-ASAT and S-ALAT activity, characteristic of delirium tremens, are secondary in importance as explaining factors to serum magnesium concentration.

These results support the concept that magnesium cation is a key factor in the biochemical lesion of alcohol disease (*Flink et al.* (1954), *Stendig-Lindberg* (1974), *Whang et al.* (1974)).

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APPENDIX

SPSS STEPWISE REGRESSION

Until 1970, the most extensively used package for statistical computing was BMD (abbreviation of BIO-MEDICAL), developed by the Center for Health Statistics at the University of California in Los Angeles. Based on this experience, and that of other less widely known packages, a group at Stanford University developed the SPSS package (Statistical Package for the Social Sciences) *Nie et al.* (1970). This package has been applied to biological data in recent years.

Both packages contain, among others, programmes for performing stepwise multiple regression. It can be safely said, after years of experience with the stepwise computing programmes, that they are error-free.

Stepwise regression (multiple-regression in which the explanatory variables are added to the model one at a time instead of all at once) is extensively used today as an ad-hoc technique for statistically screening the simultaneous effects of a large number of possible explanatory variables. The technique is described in detail in *Draper & Smith* (1966). Essentially, a preliminary calculation is made of the additional explanation given by each variable not yet in the model, and the next variable is selected to add to the model accordingly.

We repeat that the stepwise regression is an ad-hoc technique and, like all ad-hoc techniques, it therefore lacks a substantive basis. The results of a stepwise regression analysis must be reviewed in the light of substantive knowledge. In particular, the presence of correlation among the explaining variables may result in a regression coefficient whose sign (+ or –) is opposite to what would be expected logically.

DUMMY VARIABLES

The use of dummy variables to deal with qualitative variables within a quantitative (multiple regression) analysis is now very widespread. A description of the technique, as used in conjunction with multiple regression analysis, can be found in *Draper & Smith* (1966).

To illustrate the technique, suppose we are interested in the quantitative relationship between the duration of delirium tremens and serum magnesium concentration when the presence or absence of liver disease is taken into account. Instead of developing two separate relationships for duration of delirium tremens versus serum magnesium concentration, one for those with liver disease and one for those without, one quantitative relationship can be developed using two predictor variables.

Let Y = Duration of delirium tremens (quantitative)
X_1 = Serum magnesium concentration (quantitative)
X_2 = 1, if subject has liver disease
= 0, if subject does not have liver disease

Here, X_2 can be thought of as a crude measure of the "amount" of liver disease.

In the present study one of the regression results related the duration of delirium tremens to the serum magnesium concentration and liver disease. The relationship was expressed by the following equation:

Duration (var. 46) = 4.9 + 0.3 times liver disease (var. 36) – 1.8 times serum magnesium concentration (var. 21)

This equation is equivalent to two separate equations; one for those patients who have liver disease and one for those who do not.

For patients with liver disease:

Duration (var. 46) = 5.2–1.8 times serum magnesium concentration (var. 21)

and for patients without:

Duration (var. 46) = 4.9–1.8 times serum magnesium concentration (var. 21)

Both equations are shown graphically below, using six fictitious numbers for the purpose of clarification (Fig. 5).

The regression constant 4.9 estimates the duration of the reference point of 0 serum magnesium concentration and is of no substantive interest.

The estimated change in duration per unit serum magnesium concentration is given by the regression coefficient –1.8 and shown as the slope of the regression line.

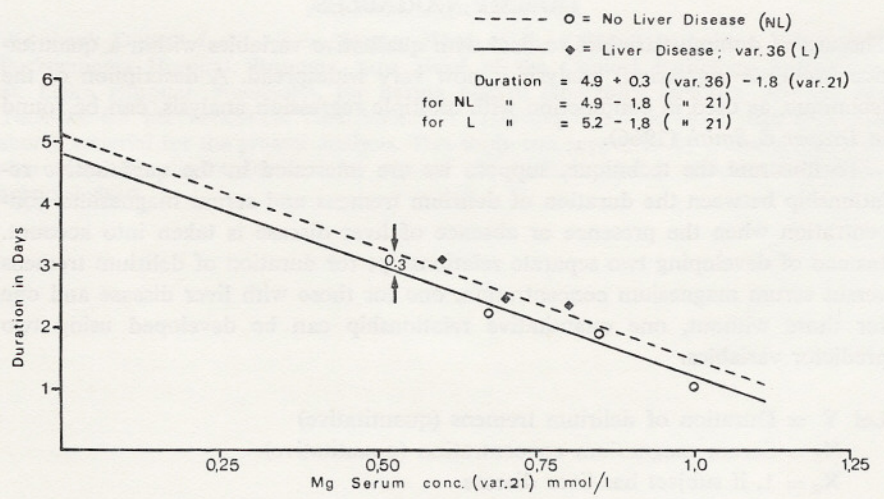

Fig. 5. *Dummy variables illustrated graphically.*

The regression coefficient of 0.3 (days) estimates the amount by which the duration of delirium tremens is increased in the presence of liver disease and is shown on the graph as the difference between the two parallel regression lines.

PERCENTAGE EXPLANATION

It is customary and convenient in multiple regression studies to refer to the degree of explanation afforded by a model in percentage terms. For ordinary multiple regression the percentage of explanation is the square of the multiple correlation coefficient. In multiple regression, in which the independent variables are uncorrelated, the percentage explanation of each independent variable is merely the square of the simple coefficient of correlation with the dependent variable.

In stepwise regression in which the independent variables may themselves be intercorrelated, the percentage explanation contributed by an independent variable is obtained from the change in total explanation produced by adding the variable to the model.

FORCING

The use of forcing, a variant of SWR, is of value when the correlations between the explaining variables are high, so that even important variables could be selected by the programme only in the last stages of the model building process. By forcing the variables of interest into the model at early stages, we insure that the fullest explaining power of the variables can manifest itself.

In the forcing procedure, the SWR was not left free to choose variables, but rather was forced to introduce in the first step of the regression a selected variable. After the first forced step, the programme was left free to select among the remaining variables. In addition, pairs of selected variables were also forced in alternation.

REFERENCES

Allgén, L.-G., S. Izikowitz, J.-B. Ordell & I. Salum (1957): Klinisk-kemiska undersökingar vid delirium tremens och s.k. predelirium. Nord. Med. *58,* 1921–1923.

Belknap, J. K., J. H. Berg & R. R. Coleman (1978): Alcohol withdrawal and magnesium deficiency in mice. Pharmacol. Biochem. Behav. *9,* 1–6.

Bonnichsen, R. K., & H. Theorell (1951): An enzymatic method for the microdetermination of ethanol. Scand. J. Lab. Invest. *3,* 58–62.

Cutshall, B. J. (1965): The Saunders-Sutton syndrome. An analysis of delirium tremens. Quart. J. Int. Alcohol *26,* 423–448.

Draper, N. R., & H. Smith (1966): Applied regression analysis. John Wiley & Sons, New York.

Dyckner, T., & P. O. Wester (1979): Ventricular extrasystoles and intracellular electrolytes before and after potassium and magnesium infusion in patients on diuretic treatment. Amer. Heart J. *97,* 12.

Flink, E. B. (1980): Clinical manifestation of acute magnesium deficiency in man. In: Magnesium in health and disease. Proceedings of the 2nd Int. Symposium on Magnesium. Spectrum Publications Inc., New York (in press).

Flink, E. B., F. L. Stutzman, A. R. Anderson, T. Konig & R. Fraser (1954): Magnesium deficiency after prolonged parenteral fluid administration and after chronic alcoholism complicated by delirium tremens. J. Lab. & Clin. Med. *43,* 169–183.

Hosein, E. A., I. Hofman & E. Linder (1977): The influence of chronic ethanol feeding to rats on the integrity of liver mitochondrial membrane as assessed with the Mg^{2+}-stimulated ATPase enzyme. Arch. Biochem. Biophys. *183,* 64–72.

Hultman, E. (1974): Metabolism of alcohol. Acta anaesth. scand., Suppl. *55,* 58–65.

Israel, Y., H. Kalant, E. Leblanc, J. C. Bernstein & I. Salazar (1970): Changes in cation transport (Na + K)-activated adenosine triphosphatase produced by chronic administration of ethanol. J. Pharm. Exp. Therap. *174,* 330–336.

Jones, J. E., S. R. Shane, W. H. Jacobs & E. B. Flink (1969): Magnesium balance studies in chronic alcoholism. In *Flink, E. B., & J. E. Jones* (eds.): The pathogenesis and clinical significance of magnesium deficiency. Ann. N.Y. Acad. Sci. *162,* 934–946.

Kalbfleisch, J. M., R. D. Lindeman, H. E. Ginn & W. O. Smith (1963): Effects of ethanol administration on urinary excretion of magnesium and other electrolytes in alcoholic and normal subjects. J. Clin. Invest. *4,* 1471–1475.

Lieber, C. S. (1975): Interference of ethanol in hepatic cellular metabolism. In *Seixas, F. A., K. Williams, & S. Eggleston* (eds.): Medical consequences of alcoholism. Ann. N.Y. Acad. Sci. *252,* 24–50.

Lindenman, R. D. (1969): Influence of various nutrients and hormones on urinary divalent cation excretion. In *Flink, E. B. & J. E. Jones* (eds.): The pathogenesis and clinical significance of magnesium deficiency. Ann. N.Y. Acad. Sci. *162,* 802–809.

Lundquist, F. (1975): Interference of ethanol in cellular metabolism. In *Seixas, F. A., K. Williams & S. Eggleston* (eds.): Medical consequences of alcoholism. Ann. N.Y. Acad. Sci. *252,* 11–20.

Mendelson, J. H., & N. K. Mello (1976): Behavioural and biochemical interrelations in alcoholism. Ann. Rev. Med. *27,* 321–333.

Meyer, J. G., & K. Urban (1977): Electrolyte changes after alcohol withdrawal. J. Neurol. *215,* 135–140.

Nie, N. H., D. H. Bent & C. H. Hull (1970): SPSS statistical package for the social sciences. McGraw Hill Book Co., New York.

Nielsen, J. (1965): Delirium tremens in Copenhagen. Acta psychiat. scand., Suppl. *187.*

Reed, P. W., & H. A. Lardy (1973): A 23187: a divalent cation ionophore. J. Biol. Chem. *247,* 6970–6977.

Rydberg, U. (1974): Alkoholens omsättning. Läkartidn. *71,* 943–946.

Salum, I. (1972): Delirium tremens and certain other acute sequels of alcohol abuse. A comparative clinical, social and prognostic study. Acta psychiat. scand., Suppl. *235.*

Seelig (1969): Electrographic patterns of magnesium depletion appearing in alcoholic heart disease. In *Flink, E. B., & J. E. Jones* (eds.): The pathogenesis and clinical significance of magnesium deficiency. Ann. N.Y. Acad. Sci. *162,* 906–917.

Shils, M. E. (1969): Experimental production of magnesium deficiency in man. In *Flink, E. B., & J. E. Jones* (eds.): The pathogenesis and clinical significance of magnesium deficiency. Ann. N.Y. Acad. Sci. *162,* 847–855.

Stendig-Lindberg, G. (1974): Hypomagnesaemia in alcohol encephalopathy. Acta psychiat. scand. *50,* 465–480.

Stendig-Lindberg, G., J. Bergström & E. Hultman (1977): Hypomagnesaemia and muscle electrolytes and metabolites. Acta med. scand. *201,* 273–280.

Suter, C., & W. O. Klingman (1955): Neurologic manifestations of magnesium depletion states. Neurology (Minneapolis) *5,* 691–699.

Szelényi, J. (1973): Magnesium and its significance in cardiovascular and gastro-intestinal disorders. Wld Rev. Nutr. Diet. *17,* 189–224.

Thiers, R. E., & B. L. Vallee (1957): Distribution of metals in subcellular fractions of rat liver. J. Biol. Chem. *226,* 911–920.

Vallee, B. L., W. E. C. Wacker & D. D. Ulmer (1960): The magnesium deficiency tetany syndrome in man. New Engl. J. Med. *262,* 155–161.

Wadstein, J., & G. Skude (1978): Does hypokalaemia precede delirium tremens? Lancet *ii*, 549–550.

Whang, R., M. P. Ryan & J. K. Aikawa (1974): Delirium tremens: a clinical example of cation pump failure: Amer. J. clin. Nutr. *27*, 447–449.

Wolfe, S. M., & M. Victor (1969): The relationship of hypomagnesaemia and alkalosis to alcohol withdrawal symptoms. In *Flink, E. B., & J. E. Jones* (eds.): The pathogenesis and clinical significance of magnesium deficiency. Ann. N.Y. Acad. Sci. *162*, 973–984.

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