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# Changes of Laboratory Variables with Time in Cirrhosis: Prognostic and Therapeutic Significance

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**The time change of laboratory variables in cirrhosis was studied by analysis of data from 488 patients with cirrhosis included in a controlled clinical trial of long-term prednisone vs. placebo.**

**In the placebo group, a marked regression towards normal was seen within 3 months of entry into the trial (increase in serum albumin, acetylcholinesterase, cholesterol, hemoglobin and decrease in erythrocyte sedimentation rate). The subsequent course did not show a clear pattern, except for a slight increase in serum bilirubin and decrease in albumin. When studied in relation to the time of death in patients dying from a "hepatic" cause, marked increase in bilirubin and decrease in prothrombin index, albumin and cholesterol were seen in the year prior to death with little change before that time.**

**In the prednisone group, a more marked decrease in bilirubin, SGOT, alkaline phosphatase, γ-globulin, sulfobromophthalein retention, erythrocyte sedimentation rate and increase in leukocytes, prothrombin index and cholesterol were seen during the first 3 months. In relation to time of death from a "hepatic" cause, similar changes were seen as in the placebo group except that alkaline phosphatase increased and cholesterol did not decrease.**

**A beneficial effect of prednisone on survival, as expressed by a previously developed therapeutic index, was associated with decrease in SGOT, alkaline phosphatase and γ-globulin within the first 3 months. An increase in SGOT during prednisone seemed to be associated with harmful effects of therapy.**

In patients with cirrhosis, laboratory tests taken at the time of diagnosis may give an indication of prognosis or therapeutic effect of prednisone or both (1-3). The change in the level of laboratory tests with time has rarely been studied, but nevertheless, it is assumed that certain changes are indicators of poor prognosis (e.g., decrease in albumin, prothrombin index, increase in bilirubin) or of beneficial effect of treatment with corticosteroid hormones (decrease in SGOT and γ-globulin) (4-7).

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Corticosteroid hormones, which are effective in selected cases of chronic liver disease (3-9), have numerous metabolic effects (9, 10), and many laboratory tests commonly used in cirrhosis are affected by corticosteroids also in healthy persons (9-11).

The purpose of this work was to evaluate the changes with time in laboratory tests, the influence of steroid treatment and the correlations to previously developed indices for prediction of prognosis (2) and therapeutic effect (3) based on prospectively collected data from a multicenter controlled clinical trial with a long follow-up.

## PATIENTS AND METHODS

During the period 1962 to 1969, patients with histologically verified liver cirrhosis were included in a controlled clinical trial evaluating the effect of prednisone vs. placebo on survival (12). This report analyzes the data of 488 patients whose initial biopsy permitted histologic

reevaluation using updated, more restrictive criteria (13). With these criteria, cirrhosis was confirmed in 287 patients (59%), probable in 101 (21%), compatible in 89 (18%) and unlikely in 11 (2%) (13). The mean age of the patients was 59 years, and 40% were females. The allocation was based on date of birth, 251 receiving prednisone and 237 placebo. Of the 488 patients, 208 (prednisone 114, placebo 94) were alcoholics. The dosage of prednisone was initially 40 mg per day being reduced during 1 to 2 months to a dose of 10 to 15 mg per day. During the trial period (up to September, 1974), 292 of the 488 patients died, 142 in the prednisone group ["hepatic main cause" (hepatic failure, GI bleeding and primary liver carcinoma) in 94, "nonhepatic" main cause (mainly cardiovascular disease, extrahepatic malignancy and infection) in 48] and 150 in the placebo group ("hepatic" cause in 91, "nonhepatic" in 59) (14). Death from surgery for bleeding varices and death from bleeding peptic ulcers were considered hepatic (1, 14). The cumulative survival curves of the two groups are shown in Figure 1.

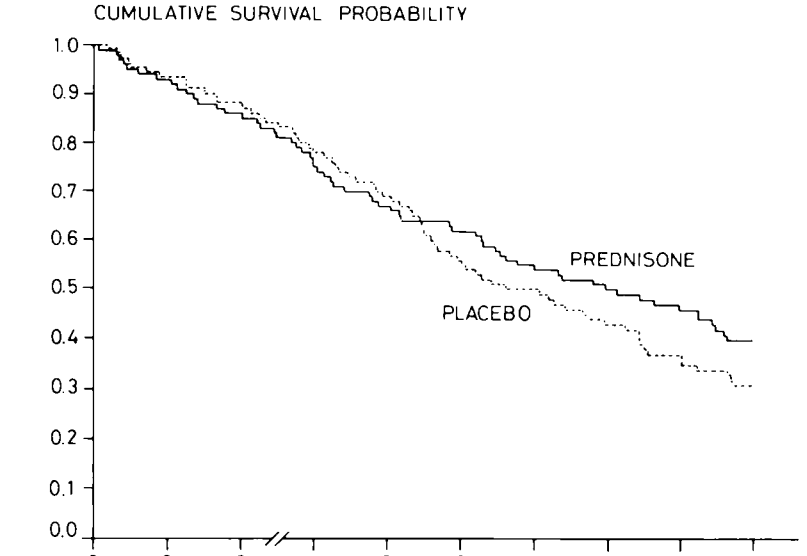
Laboratory tests were scheduled to be made at entry into the trial, at 3, 6, 12 months and yearly thereafter. Accordingly, the observation period was divided into the following intervals: 0–1.4 months; 1.5–4.4 months; 4.5–8.9 months; 9.0 months–1.4 years; 1.5–2.4 years; 2.5–3.4 years, and so on.

In each interval, data were summarized by estimation of the mean, standard deviation (S.D.) or coefficient of variation in percent (CV = 100 × mean/S.D.). In case of a skewed distribution of values, the estimations and the statistical tests (see below) were performed after appropriate (logarithmic) transformation of the data. If a patient had 2 or more values in an interval, these were replaced by their mean value. The distribution in time of values within each interval was also summarized by estimation of the mean and S.D. Since we wanted to study the response of the laboratory tests to the pharmacologic action of prednisone, we only studied data obtained during active treatment. Thus, data after dropout or withdrawal were not used.

To avoid the bias caused by the decrease in the number of patients observed with time, courses were analyzed in groups of patients having values in all intervals of the period studied. Thus, patients with missing data in the period were excluded. Since each patient can contribute only while being observed, patients with the shortest observation can contribute only to the first interval whereas patients with the longest observation can contribute to all intervals. Thus, the studied patient groups overlap. The first group includes all patients having data in the first interval, the last group only those with data in all intervals studied. By comparison of corresponding values in adjacent groups, this method enables estimation of the magnitude and direction of the effect of selection due to the loss of patient data with time from any cause including death. An example of this will be given in the results.

Since the onset of disease is poorly defined by the time of entry into the study and since the greatest changes occurred in the year prior to death, the course was also studied in relation to time of death summarizing data in the following intervals: 0–0.4 years; 0.5–1.4 years; 1.5–2.4 years, and so on before death.

Comparison of values at two different times in the same patients were made using Student's t test for paired data, t being the ratio of the mean change to its standard error. Comparison of changes in different patients were




| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| PRED. | 251 | 221 | 196 | 163 | 138 | 120 | 97 | 87 | 75 | 55 | No. observed |
| | - | 18 | 34 | 58 | 75 | 84 | 99 | 106 | 112 | 122 | No. of deaths |
| PLAC. | 237 | 217 | 200 | 170 | 141 | 110 | 92 | 80 | 61 | 42 | No. observed |
| | - | 16 | 29 | 51 | 70 | 95 | 107 | 119 | 130 | 140 | No. of deaths |

FIG. 1. Cumulative survival curves for the prednisone and placebo groups. The difference was not significant. The number of patients observed and the cumulative number of deaths are also shown.

made using Student's t test for unpaired data using Satterthwaites' approximation in case of unequal variances (15). P values ($2\alpha$) < 0.01 were considered significant.

The relation of change of laboratory values within the first 3 months to the prognostic and therapeutic disposition was studied by estimating the product-moment correlation coefficient with a prognostic index (2) and a therapeutic index (3) defined previously. With a decreasing value of the prognostic index, prognosis improves (2). With increasing value of the therapeutic index, defined as the difference between the prognostic index calculated for placebo and prednisone treatment, respectively, the therapeutic effect of prednisone increases (3).

## RESULTS

Changes of laboratory data in relation to time of entry into the trial are shown in Table 1 and Figures 2 to 7. Table 1 summarizes the changes seen within the first 3 months in both treatment groups. (To facilitate comparison with units usually used in *Hepatology*, equivalent values if available are given in Table 2.) Significant increases in hemoglobin, albumin and acetylcholinesterase are seen irrespective of the treatment. During prednisone treatment, highly significant decreases in bilirubin, SGOT, alkaline phosphatase, $\gamma$-globulin and sulfobromophthalein retention, and significant increases in leukocytes and prothrombin index (decrease in prothrombin time) are found, in addition to a more marked increase in cholesterol and decrease in erythrocyte sedimentation rate than during placebo treatment.

The more detailed course of important laboratory variables are shown in Figures 2 to 7 in groups defined by the minimum duration of follow-up. In these figures, the standard deviations of times (in months) $SD_{time}$ after time zero are as follows: 3 months, 0.3–0.5; 6 months, 0.5–0.7; 1 year, 1.0–1.2; 2 years, 0.7–2.0; 3 years, 1.3–2.2; 4 years, 1.3–2.3; 5 years, 1.2–1.7; 6 years, 1.1–1.9, and 7 years, 1.6–2.2. In many figures, a marked change within the first 3 months is seen. Furthermore, some of the curves show that the subsequent course is far from being linear.

Bilirubin (Figure 2) (17 $\mu$moles = 1.0 mg per dl) after the first 3 months shows little change until the last year of follow-up in each particular group when an increase is often seen.

Alkaline phosphatase (Figure 3) (10 KA units = 85 IU per liter) in the prednisone group shows a marked increase after the initial drop. During placebo treatment, a weak decrease is seen with time.

SGOT (Figure 4) (1.7 mmoles per liter per hr = 40 IU per liter) shows relatively little change during prednisone treatment after the initial drop within 3 months. During placebo treatment, the decrease is slower, but ultimately the levels reach those seen in the prednisone group.

Prothrombin index (Figure 5) in the prednisone group shows slight decrease at least up to year 3 within each group after the initial marked increase. In the placebo group, levels increase up to year 1, drop slightly from year 1 to year 2, then increase slightly again. (Note: decreasing prothrombin index corresponds to increasing prothrombin time and vice versa.)

Albumin (Figure 6) (30 gm per liter = 3 gm per dl) shows some increase up to year 1 in the groups with long observation periods, but the last part of the course tends to decrease in each group especially during prednisone treatment.

$\gamma$-Globulin (Figure 7) (15 gm per liter = 1.5 gm per dl) in the prednisone group is rather constant for the first 3 years after the marked initial drop, thereafter levels tend to increase. During placebo treatment, levels tend to decrease slowly but in the last year, in patients being followed for 3 years or more, weak increases are found.

TABLE 1. CHANGE IN LABORATORY VARIABLES DURING THE FIRST 3 MONTHS AFTER ENTRY INTO THE TRIAL

| Variable (normal values) | Prednisone n | Prednisone Mean change | Prednisone t | Placebo n | Placebo Mean change | Placebo t | p for difference |
|---|---|---|---|---|---|---|---|
| Hemoglobin (7.0–11.0 mmoles/liter) | 188 | 0.50 | 5.89* | 175 | 0.38 | 4.72* | 0.29 |
| Erythrocyte sedimentation rate (<10 mm/hr) | 183 | −18.2 | 8.89* | 176 | −10.4 | 5.08* | 0.007 |
| Leukocytes[a] (3.0–9.0 × $10^9$/liter) | 167 | 1.12 | 4.32* | 157 | 0.06 | 0.32 | 0.003 |
| Thrombocytes[a] (150–350 × $10^9$/liter) | 166 | −1.72 | 0.25 | 161 | −0.45 | 0.06 | 0.89 |
| Bilirubin[a] (4–22 $\mu$moles/liter) | 177 | −6.03 | 4.92* | 171 | 0.09 | 0.11 | <0.001 |
| SGOT[a] (<1.7 mmoles/liter/hr) | 193 | −1.13 | 5.73* | 178 | −0.21 | 1.00 | <0.001 |
| Alkaline phosphatase[a] (<10 KA units) | 192 | −2.41 | 4.66* | 182 | −0.21 | 0.36 | 0.002 |
| Acetylcholinesterase (2.0–6.1 $\mu$moles/ml/min) | 146 | 0.38 | 4.84* | 137 | 0.35 | 3.90* | 0.80 |
| Prothrombin index (>70% of normal) | 189 | 14.4 | 8.37* | 182 | −0.27 | 0.19 | $<10^{-8}$ |
| Albumin (>44 gm/liter) | 181 | 3.89 | 6.60* | 178 | 3.30 | 5.28* | 0.50 |
| $\gamma$-globulin[a] (<11 gm/liter) | 179 | −4.14 | 9.39* | 175 | −0.32 | 0.75 | $<10^{-8}$ |
| Cholesterol[a] (3.4–7.8 mmoles/liter) | 143 | 1.08 | 7.03* | 137 | 0.43 | 2.85** | 0.006 |
| Sulfobromophthalein retention (<5% after 45 min) | 88 | −7.51 | 5.23* | 68 | −2.60 | 1.98 | 0.01 |

[a] The statistical tests were performed on transformed values (logarithmic transformation); the mean change given is the difference between antilogs of means of logarithmic values.

* $p < 0.001$.

** $p < 0.01$.

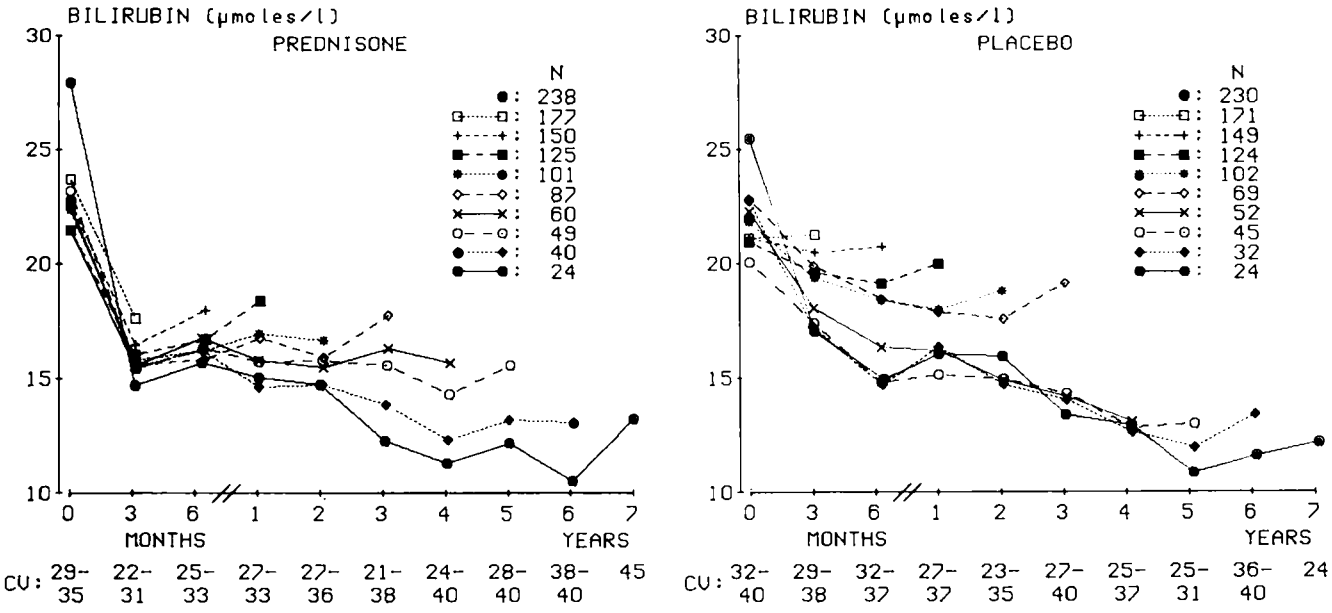



FIG. 2. Course of bilirubin in relation to time of entry into the trial in overlapping groups with complete data in each period of observation. Antilogs of means of logarithmic values are presented. N, number of patients; CV, coefficient of variation of logarithmic values. Note: levels are expressed in μmoles per liter (17 μmoles per liter = 1.0 mg per dl).

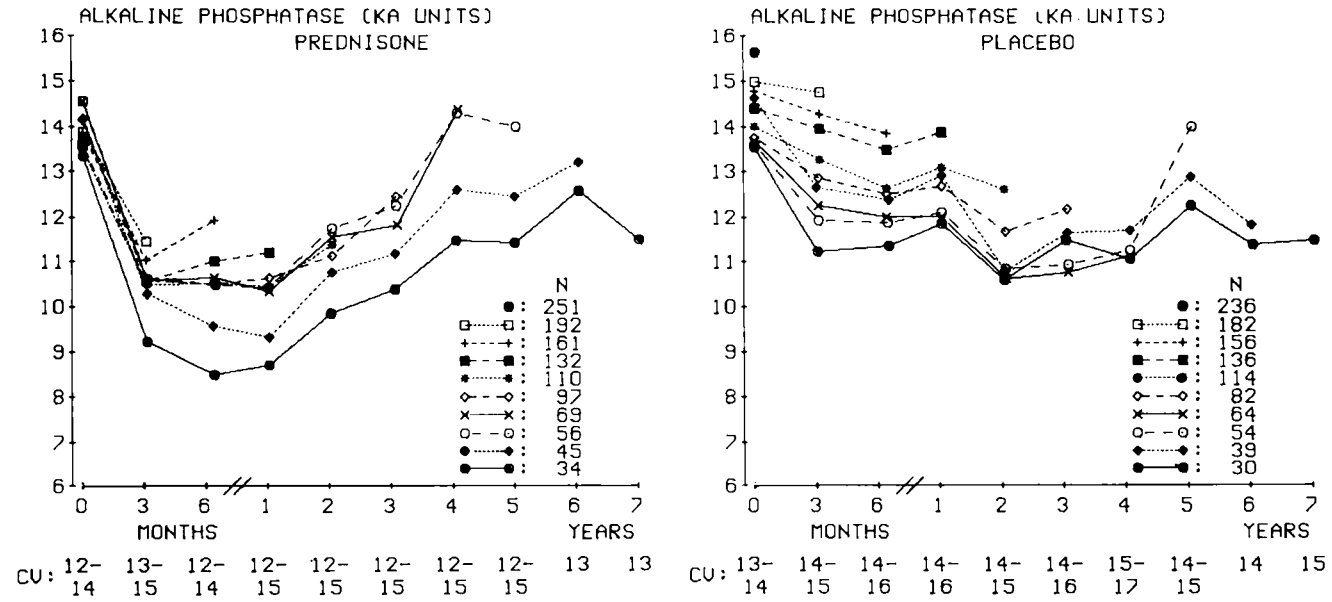



FIG. 3. Course of alkaline phosphatase in relation to time of entry into the trial in overlapping groups with complete data in each period of observation. Antilogs of means of logarithmic values are presented. N, number of patients. CV, coefficient of variation of logarithmic values. Note: levels are expressed in KA units (10 KA units = 85 IU per liter).

The effect of selection caused by loss of patients (from any cause including death) with time can be read from the figures by comparing corresponding levels in adjacent groups. The selection effect is most clearly seen in the curves for bilirubin (Figure 2), prothrombin index (Figure 5) and albumin (Figure 6), where the level of each subsequent group (with longer observation) is less abnormal than that of the preceding group at the same time of observation.

*Example.* Considering albumin in the prednisone group (Figure 6, left) at 6 months in the 149 patients with data up to that time [mean = 40.6 gm per liter (=4.06 gm per dl)] and in the 124 patients with data up to year 1 [mean = 42.1 gm per liter (=4.21 gm per dl)], the mean value at 6 months in the 25 lost patients (149–124) can be estimated to 33.16 gm per liter (=3.316 gm per dl) [(149 × 40.6 - 124 × 42.1)/25], suggesting that these lost 25 were among the more severely ill patients.

## ALCOHOLIC VS. NONALCOHOLIC PATIENTS

During placebo treatment, the initial regression towards normal in erythrocyte sedimentation rate and

acetylcholinesterase was significantly more pronounced in the alcoholic than in the nonalcoholic patients.

During prednisone treatment, the initial decrease in SGOT, alkaline phosphatase and increase in leukocytes and cholesterol were significantly more pronounced in the nonalcoholic than in the alcoholic patients. Otherwise, courses were similar in alcoholic and nonalcoholic patients.

## Course in Relation to Time of Death

Analysis of the course in relation to time of death revealed that the major changes occurred in the year prior to death of hepatic cause. The change of variables in the last year before death studied by comparing values in the adjacent intervals 1.4–0.5 years and 0.4–0 years before death in patients with values in both intervals are shown in Table 3 and Figures 8 to 10, which also show the levels in earlier intervals. In these figures, the standard deviations of times (in months) within the defined intervals, $SD_{time}$, were as follows: 0 years, 1.3–1.7; 1 year, 2.0–3.4; 2 years, 2.5–2.8, and 3 years, 2.4–2.7. The significant changes were confined to patients who died from a hepatic cause (Table 3). Significant increase in bilirubin (Figure 8) and decrease in albumin (Figure 9) were

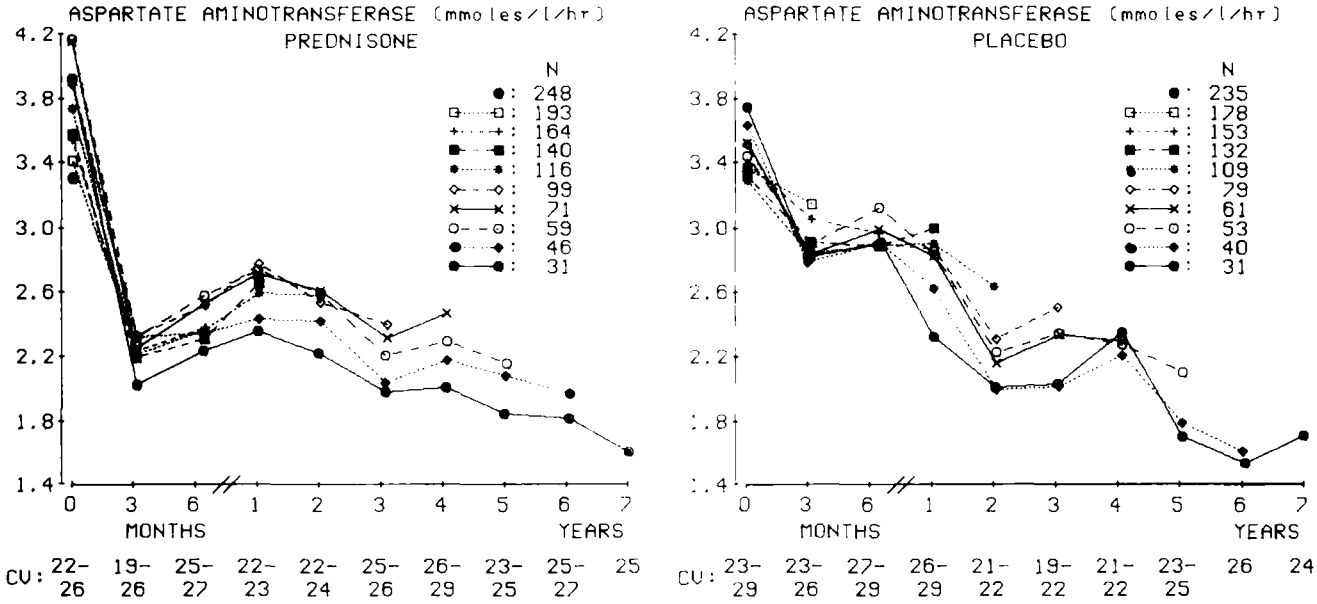



FIG. 4. Course of SGOT (aspartate aminotransferase) in relation to time of entry into the trial in overlapping groups with complete data in each period of observation. Antilogs of means of logarithmic values are presented. N, number of patients. CV, coefficient of variation of logarithmic values. Note: levels are expressed in mmoles per liter per hr (1.7 mmoles per liter per hr = 40 IU per liter).

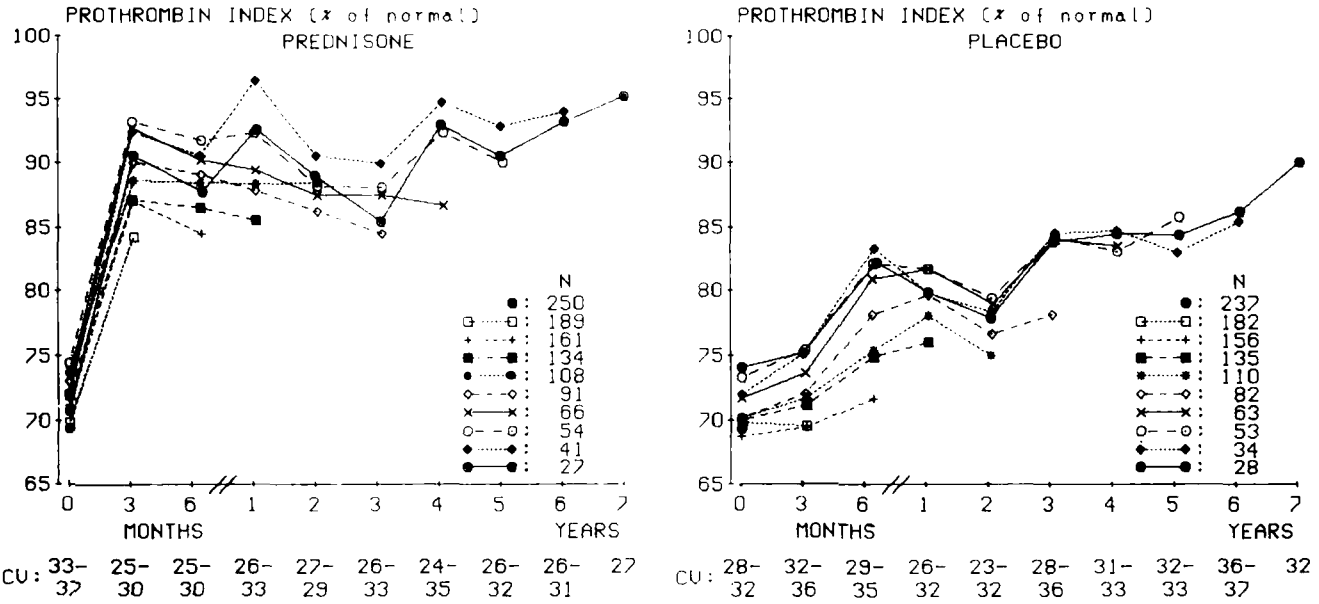



FIG. 5. Course of prothrombin index in relation to time of entry into the trial in overlapping groups with complete data in each period of observation. N, number of patients. CV, coefficient of variation. Note: levels are expressed as an index, not as the prothrombin time.

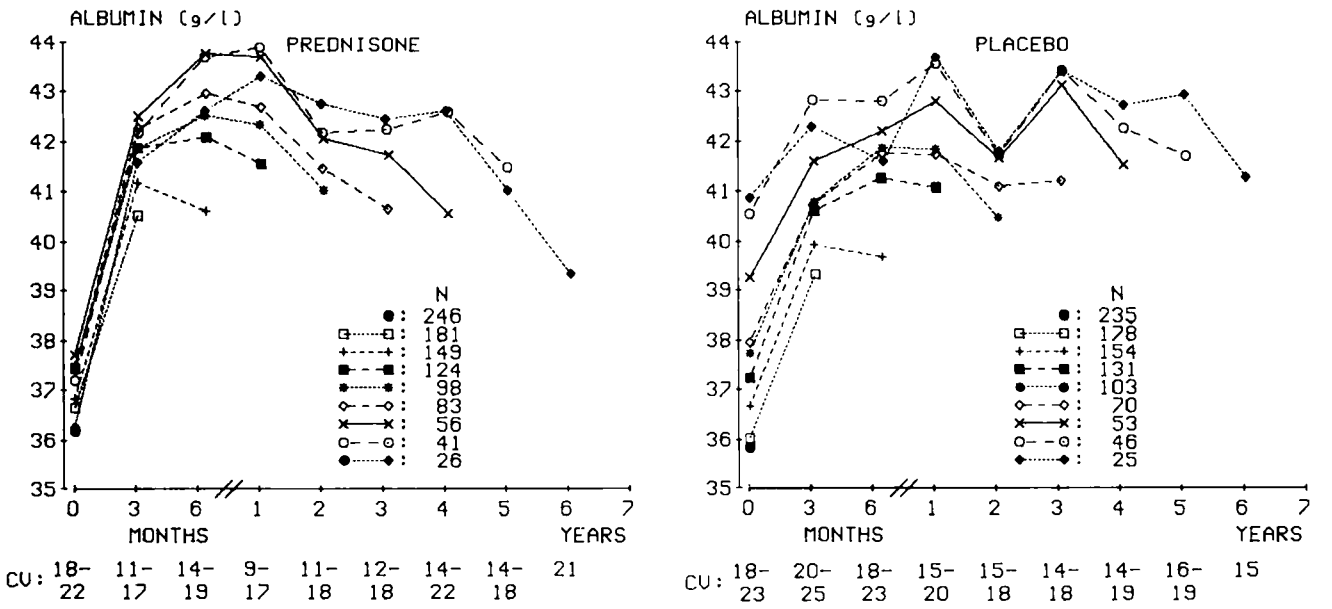



FIG. 6. Course of albumin in relation to time of entry into the trial in overlapping groups with complete data in each period of observation. N, number of patients. CV, coefficient of variation. Note: levels are expressed in grams per liter (30 gm per liter = 3 gr per dl).

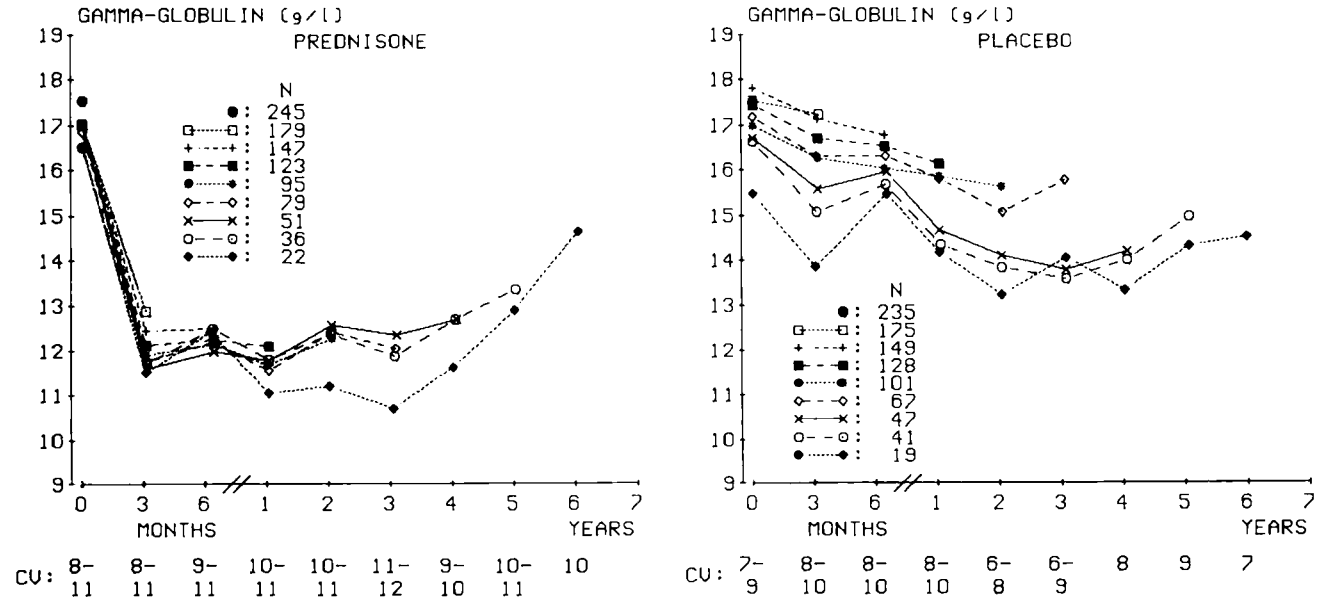



FIG. 7. Course of γ-globulin in relation to time of entry into the trial in overlapping groups with complete data in each period of observation. Antilogs of means of logarithmic values are presented. N, number of patients. CV, coefficient of variation of logarithmic values. Note: levels are expressed in grams per liter (15 gm per liter = 1.5 gm per dl).

seen. Prothrombin index (Figure 10) decreased (prothrombin time increased) (significantly in the placebo group) (Table 3). Acetylcholinesterase showed a similar decrease not quite significant, and hemoglobin decreased (significantly in the prednisone group) (Table 3). During prednisone treatment, alkaline phosphate increased, and during placebo treatment cholesterol decreased and γ-globulin increased significantly in the year prior to death from a hepatic cause (Table 3). However, none of the differences between the two treatment groups were significant. The pattern was rather similar in alcoholic and nonalcoholic patients.

## CORRELATION OF INITIAL CHANGE WITH THERAPEUTIC AND PROGNOSTIC DISPOSITION

In Table 4 are shown coefficients of correlation between the change in laboratory variables within the first 3 months and the patients' therapeutic and prognostic indices, respectively, being estimates of the patients' therapeutic and prognostic disposition at the time of entry into the trial (2, 3).

During prednisone treatment, the initial changes in SGOT, γ-globulin and alkaline phosphatase (the latter two only in nonalcoholic patients) are negatively corre-

lated with the therapeutic index, showing that decrease in these variables is associated with positive values of the therapeutic index indicative of beneficial effect of prednisone treatment. Furthermore, during prednisone therapy, the changes in SGOT and cholesterol (the latter only in alcoholic patients) are positively correlated with the prognostic index, showing that increase in these variables is associated with high (positive) values of the prognostic index indicative of poor prognosis.

During placebo treatment, the change in leukocytes (in nonalcoholic patients) is positively correlated with the therapeutic index, suggesting that increase in leukocytes is associated with a potentially beneficial effect of prednisone therapy, indicating that this should be considered. None of the variables which correlated significantly with prognostic index or therapeutic index contributed to the index in question (2, 3). However, all significant correlations were small indicating that the changes in single variables have relatively little prognostic or therapeutic value.

TABLE 2. EQUIVALENT VALUES OF LABORATORY VARIABLES

| | |
|---|---|
| Hemoglobin | 7.0 mmoles/liter = 11.3 gm/dl |
| Leukocytes | $3.0 \times 10^9$/liter = 3000/$\mu$l |
| Thrombocytes | $150 \times 10^9$/liter = 150000/$\mu$l |
| Bilirubin | 17 $\mu$moles/liter = 1.0 mg/dl |
| SGOT | 1.7 mmoles/liter/hr = 40 IU/liter |
| Alkaline phosphatase | 10 KA units = 85 IU/liter |
| Acetylcholinesterase | 2.0 $\mu$moles/ml/min = 525 IU/liter |
| Albumin | 30 gm/liter = 3 gm/dl |
| $\gamma$-globulin | 15 gm/liter = 1.5 gm/dl |
| Cholesterol | 7 mmoles/liter = 270 mg/dl |

## DISCUSSION

Description of change in time of variables from controlled clinical trials of chronic disease requiring long periods of observation may not be simple because the number of patients decreases with time. Thus, studying the course by simple transection analysis at certain intervals may be biased by the loss of patients with time. However, that method has been used in several reports (5–7). Trend analysis estimating the slope by linear regression on the values in each patient may be misleading because the course may be nonlinear even after transformation of values. That seemed to be the case for many of the variables (Figures 2 to 7). Thus, results obtained by that method can only be taken as crude indications of the course. Therefore, we did not use trend analysis in this report.

To avoid bias caused by decreasing number of patients

TABLE 3. CHANGE IN LABORATORY VARIABLES BETWEEN THE INTERVALS 1.5–0.5 AND 0.5–0 Years Before Death

| Variable (normal values) | Cause of death | Prednisone n | Prednisone Mean change | Prednisone t | Placebo n | Placebo Mean change | Placebo t | p for difference |
|---|---|---|---|---|---|---|---|---|
| Hemoglobin | H[a] | 32 | −0.68 | 3.27* | 39 | −0.54 | 2.71 | 0.63 |
| (7.0–11.0 mmol/liter) | N-H[b] | 14 | −0.45 | 1.45 | 22 | 0.22 | 0.75 | 0.12 |
| Erythrocyte sedimentation | H | 32 | 1.03 | 0.25 | 38 | 8.76 | 2.67 | 0.14 |
| rate (<10 mm/hr) | N-H | 13 | −5.74 | 0.65 | 22 | −6.13 | 0.90 | 0.97 |
| Leukocytes[c] | H | 29 | 1.17 | 1.19 | 31 | 0.36 | 0.51 | 0.65 |
| (3.0–9.0 × $10^9$/liter) | N-H | 12 | 3.57 | 1.51 | 20 | −0.08 | 0.10 | 0.16 |
| Thrombocytes[c] | H | 29 | −12.8 | 0.73 | 31 | 5.56 | 0.32 | 0.52 |
| (150–350 × $10^9$/liter) | N-H | 11 | −23.4 | 0.57 | 20 | −17.1 | 0.62 | 0.90 |
| Bilirubin[c] | H | 52 | 16.6 | 4.26** | 61 | 20.9 | 3.49** | 0.83 |
| (4–22 $\mu$moles/liter) | N-H | 23 | 0.78 | 0.22 | 34 | 1.52 | 0.76 | 0.79 |
| SGOT[c] | H | 52 | 0.15 | 0.35 | 61 | 0.09 | 0.20 | 0.91 |
| (<1.7 mmole/liter/hr) | N-H | 24 | 0.26 | 0.71 | 38 | −0.02 | 0.12 | 0.52 |
| Alkaline phosphatase[c] | H | 55 | 5.71 | 3.32* | 60 | 2.12 | 1.21 | 0.07 |
| (<10 KA units) | N-H | 23 | −1.92 | 0.77 | 37 | 0.57 | 0.39 | 0.60 |
| Acetylcholinesterase | H | 27 | −0.41 | 2.52 | 27 | −0.44 | 2.56 | 0.89 |
| (2.0–6.1 $\mu$moles/ml/min) | N-H | 9 | −0.05 | 0.17 | 18 | −0.19 | 0.82 | 0.74 |
| Prothrombin index | H | 52 | −9.76 | 2.54 | 58 | −8.62 | 3.39* | 0.79 |
| (>70% of normal) | N-H | 23 | 1.22 | 0.27 | 36 | 2.94 | 0.84 | 0.76 |
| Albumin | H | 45 | −3.95 | 3.54** | 50 | −4.03 | 3.53** | 0.96 |
| (>44 gm/liter) | N-H | 21 | −2.98 | 2.21 | 32 | −1.29 | 0.94 | 0.39 |
| $\gamma$-globulin[c] | H | 42 | 1.66 | 1.08 | 47 | 4.55 | 2.66 | 0.32 |
| (<11 gm/liter) | N-H | 21 | −0.01 | 0.01 | 30 | −2.05 | 2.08 | 0.25 |
| Cholesterol[c] | H | 24 | −0.18 | 0.27 | 26 | −1.72 | 3.63* | 0.03 |
| (3.4–7.8 mmoles/liter) | N-H | 10 | −0.34 | 0.34 | 19 | −0.89 | 1.57 | 0.66 |
| Sulfobromophthalein | H | 15 | 0.23 | 0.06 | 9 | −0.11 | 0.06 | 0.94 |
| retention (<5% after 45 | N-H | 6 | 1.25 | 0.51 | 8 | 2.45 | 0.61 | 0.80 |
| min) | | | | | | | | |

[a] H, hepatic main cause of death.

[b] N-H, nonhepatic main cause of death.

[c] The statistical tests were performed on transformed values (logarithmic transformation); the mean change given is the difference between antilogs of means of logarithmic values.

* $p < 0.01$.

** $p < 0.001$.

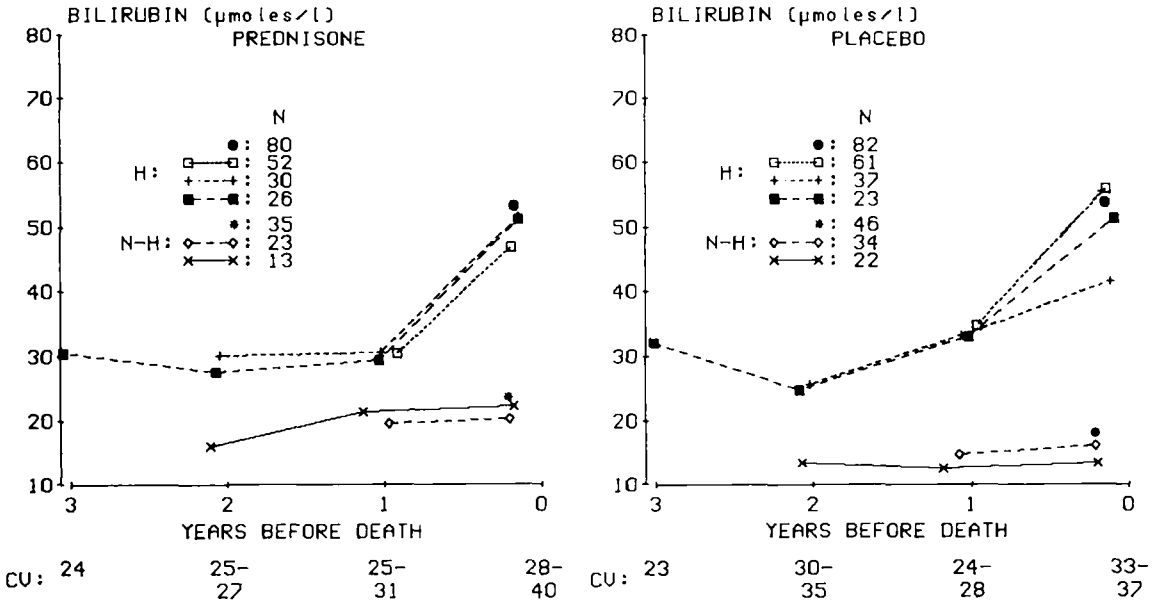



FIG. 8. Course of bilirubin in relation to time of death in overlapping groups with complete data in each period of observation. Antilogs of means of logarithmic values are presented. N, number of patients. CV, coefficient of variation of logarithmic values. Note: levels are expressed in μmoles per liter (17 μmoles per liter = 1 mg per dl).

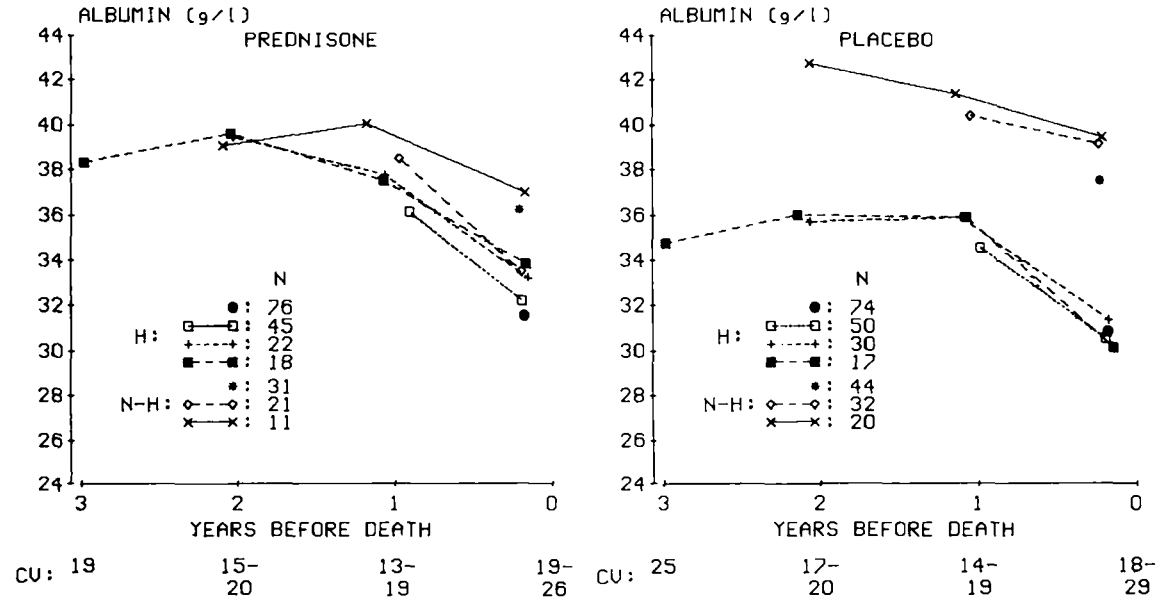



FIG. 9. Course of albumin in relation to time of death in overlapping groups with complete data in each period of observation. N, number of patients. CV, coefficient of variation. Note: levels are expressed in grams per liter (30 gm per liter = 3 gm per dl).

with time, study of the course was performed in groups of patients having values in each of the intervals making up each period of observation (Tables 1 and 3 and Figures 2 to 10). The patients having the shortest observation can contribute to only one interval, those having the longest observation times can contribute to all intervals. Thus the groups overlap, each group including patients with observation time equal to or greater than that being investigated. Thus, patients with missing observations within a given period were not included for that period. This explains the reduced number of patients studied compared to that being observed (Figure 1).

The method has the advantage that the magnitude and direction of the effect of selection due to the decreasing number of patient data with time can be estimated by comparison of corresponding values in adjacent groups. For many variables, e.g., bilirubin, alkaline phosphatase, prothrombin index and albumin, there was a tendency towards less abnormal values with increasing observation time of the group, indicating that those who were lost (from any cause including death) had relatively more abnormal values. This can be seen most clearly by comparing the last value of a group with the corresponding value in the following group as in the example in "Results."

With this method, a marked "regression towards nor-

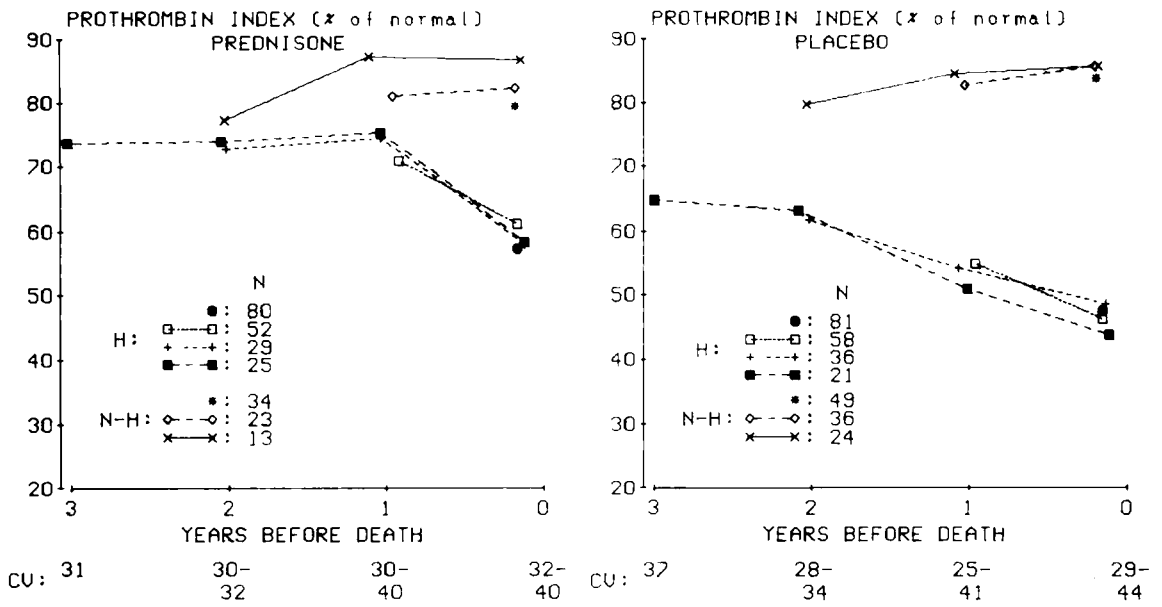



FIG. 10. Course of prothrombin index in relation to time of death in overlapping groups with complete data in each period of observation. N, number of patients. CV, coefficient of variation. Note: levels are expressed as an index, not as the prothrombin time.

mal" was demonstrated in many variables within the first 3 months in both treatment groups. This probably reflects that most patients are admitted to the hospital and the diagnosis made during an exacerbation of the disease (16). However, the subsequent course studied by this method in relation to entry into the trial (Figures 2 to 7) was less clear probably because the courses were not "synchronized" to that time and because of different reasons for short observation. By "synchronizing" the course in relation to time of death, a clearer picture was obtained, at least in patients dying from a hepatic cause (Figures 8 to 10 and Table 3).

The changes in the placebo group reflecting the "spontaneous" course comprised significant improvement within the first 3 months of entry into the trial as evidenced by an increase in albumin, acetylcholinesterase, cholesterol, hemoglobin and decrease in erythrocyte sedimentation rate. From the detailed course, marked short-term reversibility is also seen for bilirubin (Figure 2) and SGOT (Figure 4) in patients with long observation, even though their initial values are among the highest. Alkaline phosphatase also show early regression in patients with long observation (Figure 3). This short-term reversibility indicates that levels after a few months may better reflect the degree of permanent liver damage than initial levels.

The subsequent course as demonstrated by Figures 2 to 7 revealed for bilirubin that besides the increase in the last year of observation in patients observed up to 3 years, levels decrease in patients followed for longer periods. Similarly albumin levels remain relatively high and prothrombin index tends to increase (prothrombin time to decrease) in patients followed for more than 3 years. Thus, long-term improvement seems to occur in some patients.

By studying the course in relation to time of death from hepatic cause (Figures 8 to 10 and Table 3), marked increase in bilirubin and decrease in prothrombin index (increase in prothrombin time), albumin, acetylcholinesterase and cholesterol were seen. These changes all reflect decreasing hepatocellular function prior to death as one would expect. However, it is interesting to note, that the major changes occurred in the year prior to death with little change in level before that time, except perhaps for prothrombin index which show a decrease (prothrombin time increase) over 2 years before death. This rather stationary course followed by a fast accelerative fatal deterioration emphasizes the acute nature of the late stage disease.

Nevertheless, some of these variables at the time of

TABLE 4. COEFFICIENTS OF CORRELATION BETWEEN CHANGE IN LABORATORY VARIABLES DURING THE FIRST 3 MONTHS AND PREVIOUSLY DEFINED THERAPEUTIC INDEX AND PROGNOSTIC INDEX

| Variable | Therapeutic index | | Prognostic index | |
|---|---|---|---|---|
| | Prednisone | Placebo | Prednisone | Placebo |
| Hemoglobin | 0.06 | −0.06 | −0.05 | −0.06 |
| Erythrocyte sedimentation rate | 0.00 | 0.12 | 0.01 | 0.14 |
| Leukocytes[a] | 0.08 | 0.22*,[b] | −0.01 | 0.17 |
| Thrombocytes[a] | 0.08 | −0.01 | −0.12 | 0.03 |
| Bilirubin[a] | −0.14 | 0.09 | 0.09 | 0.10 |
| SGOT[a] | −0.41**,[c] | 0.01 | 0.21*,[c] | 0.03 |
| Alkaline phosphatase[a] | −0.25**,[b] | 0.00 | 0.17 | 0.11 |
| Acetylcholinesterase | 0.02 | −0.04 | 0.06 | −0.03 |
| Prothrombin index | 0.18 | −0.11 | −0.07 | 0.00 |
| Albumin | 0.13 | −0.06 | 0.03 | 0.00 |
| γ-globulin[a] | −0.30**,[b] | 0.12 | 0.17 | 0.10 |
| Cholesterol[a] | 0.13 | 0.01 | 0.22*,[d] | 0.11 |
| Sulfobromophthalein retention | −0.08 | 0.04 | −0.08 | −0.03 |

[a] The change in transformed values (logarithmic transformation) has been used in the calculation.
[b] Significant only in nonalcoholic patients.
[c] Significant both in alcoholic and nonalcoholic patients.
[d] Significant only in alcoholic patients.
* $p < 0.01$.
** $p < 0.001$.

entry into the trial had significant prognostic information as evidenced by their contribution to the prognostic index (2) (prothrombin index, acetylcholinesterase) or the Child-Turcotte criteria (1) (bilirubin, albumin), probably because a large proportion of patients died within the first year of entry into the trial (Figure 1).

It is remarkable, however, that the change within 3 months during placebo treatment did not correlate significantly with prognostic disposition as expressed by the prognostic index (Table 4). The explanation is probably that the magnitude of the initial change varies relatively little with the observation period (Figures 2 to 7).

The effects of prednisone within the first 3 months were a more marked decrease in bilirubin, SGOT, alkaline phosphatase, γ-globulin, sulfobromophthalein retention, erythrocyte sedimentation rate and increase in leukocytes, prothrombin index and cholesterol. Some of these changes are at least partly due to the metabolic effect of the corticosteroid hormone [cholesterol (17–19), prothrombin index (10, 20), bilirubin (10, 11, 21)], others to the antiinflammatory [leukocytes (22–24)] and immunosuppressive effects [erythrocyte sedimentation rate, γ-globulin (23–25)]. The decrease in SGOT, and to a lesser degree of alkaline phosphatase (26), may indicate a decreased destruction of liver cells. The increase in albumin (27) and acetylcholinesterase (28, 29) and the decrease in sulfobromophthalein retention (30) may indicate a general improvement in hepatocellular function as an indirect effect of the hormone (9), probably mainly confined to those categories known to benefit from prednisone treatment (3–9) including selected cases of chronic aggressive hepatitis (3) and alcoholic hepatitis (3, 8).

The subsequent course during prednisone treatment (Figures 2 to 7) was similar to that during placebo except that levels of prothrombin index were higher (prothrombin time shorter), levels of γ-globulin lower and alkaline phosphatase levels increased markedly with time.

When analyzed in relation to time of death, the changes seen during prednisone corresponded rather closely to those seen during placebo except for alkaline phosphatase which increased and cholesterol which did not decrease prior to death from hepatic cause, the latter possibly because of a sustained metabolic effect of the steroid hormone (17–19). The former finding is difficult to explain and may be accidental [the increase is not significantly different from that found in the placebo group, $p = 0.07$ (Table 3)].

Some of the initial changes were associated with prognostic and therapeutic disposition (Table 4) as expressed by previously developed prognostic and therapeutic indices (2, 3). Thus, we found that the initial change in SGOT, γ-globulin and alkaline phosphatase (the latter two only in nonalcoholic patients) during prednisone treatment correlates with the therapeutic index in such a way that decreases in these variables suggest beneficial effect of prednisone. (These variables do not contribute to the therapeutic index.) Furthermore, increasing SGOT during prednisone treatment seems to indicate poor prognosis (positive correlation with the prognostic index). These findings confirm that for these tests, the initial changes during prednisone treatment may indicate whether prednisone is of benefit to a patient or not (4). This may help therapeutic decision in atypical patients. It should be noted that the level in these tests at entry into the trial did not provide any significant therapeutic information (3).

We also found the initial increase in leukocytes (during placebo treatment) to be associated weakly with a potentially beneficial effect of prednisone [positive correlation with the therapeutic index (only significant in nonalcoholic patients)] (Table 4). The increase in leukocytes may reflect actively progressing disease (e.g., chronic aggressive hepatitis) where prednisone may be effective in selected cases (3, 8). Furthermore, increasing cholesterol during prednisone treatment seems associated with poor prognosis in the alcoholic patients (positive correlation with the prognostic index). The reason for this is unknown, and the correlation may be accidental since the level of significance is not very high. The proportion of deaths from cardiovascular disease was similar in the two treatment groups (14).

This report has confirmed the value of the commonly used laboratory tests in chronic liver disease. The results indicate, however, that the tests should be used selectively depending on the clinical situation and not routinely. Values on admission to hospital may be less informative than later "steady-state" values because many tests may regress markedly following the acute phase which necessitated hospitalization. Fatal deterioration runs a short accelerative course in the last year before death with little indication of decreasing liver function before that time. Albumin, bilirubin, prothrombin index and acetylcholinesterase seem the most useful tests in monitoring prognosis. These results are in agreement with a recent multivariate analysis utilizing follow-up information for updating prognosis and estimates of therapeutic effect (Christensen, E. et al., unpublished observations).

Furthermore, this report has revealed that the initial changes (in contrast to the levels) in SGOT, γ-globulin and alkaline phosphatase after start of prednisone treatment are associated with the treatment effect. This may help therapeutic decision in atypical patients [with insignificant therapeutic index (3)] by studying the short-term response to prednisone treatment. However, since our results have been obtained by retrospective analysis of the data, they should be confirmed by a controlled clinical trial including such patients [having an insignificant therapeutic index (3)], where randomization to prednisone or placebo is performed after a period of pretreatment with prednisone in all such patients.

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