Characterization of Biochemical and Clinical Correlates of Hypocholesterolemia after Hepatectomy, Ivo Giovanni
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Although hypocholesterolemia in posttraumatic states is considered a generic expression of acute-phase response, a relationship between severity of hypocholesterolemia and bad prognosis has also been found (1–6). The issue is still poorly understood and is complicated by the circumstance that plasma cholesterol is affected simultaneously by multiple factors whose impacts have never been distinctly characterized. The postoperative state after hepatec-
tomy is an interesting condition in which most of these factors may be simultaneously present. We have assessed in detail the main biochemical and clinical correlates of hypocholesterolemia in a large group of patients undergoing hepatectomy.

Hepatectomies were performed in 92 patients (47 women, 45 men). The mean (± SD) age was 57 ± 12 years, body weight was 70 ± 11 kg, the ratio of actual to ideal body weight was 1.13 ± 0.16 (1983 Metropolitan Tables), body surface area was 1.78 ± 0.15 m², and body mass index (weight/height²) was 25.0 ± 4.0 kg/m². Thirty-six patients had primary liver malignancy (23 with hepatocarcinoma, 10 with cholangiocarcinoma, 3 with other neoplasms), 35 had secondary hepatic malignancies (23 from colorectal cancer, 12 from other sources), and 21 had benign lesions. Eighteen patients had liver cirrhosis. Fifty-four patients were in ASA class I (7), 7 in class II, 30 in class III, and 1 in class IV. No patient was on cholesterol-lowering medication. Hepatectomies consisted of 43 minor (<3 liver segments) and 49 major resections (3–6 segments). The mean number of resected segments was 3 ± 1. There were 17 associated bowel operations (resec-
tions for primary malignancy or Roux-en-Y biliary recon-
structions). The duration of the operations was 390 ± 149
min, and the duration of normothermic liver ischemia (used in 61 patients) was 49 ± 28 min.

Seventy-one patients recovered without complications, whereas 15 had nonlethal complications: 9 had intra-
abdominal or pulmonary sepsis, 5 had transient liver insufficiency, and 1 had a biliary fistula without sepsis. Diagnosis of sepsis was based on previously defined criteria (5). Six patients died. The study was carried out prospectively except for the inclusion of three nonsurvivors observed outside the prospective period; this improved the significance of results in nonsurvivors without bias because the pattern of death was similar in all cases (systemic sepsis with liver and/or respiratory insuffi-
ciency, progressing to multiple organ dysfunction syn-
drome). This patient population provided a continuous distribution of observations from minor to extreme surgical procedures (and degrees of postoperative illness) suited to assess correlates of hypocholesterolemia over a wide range of pathophysiologic abnormalities.

The database included 478 venous blood measure-
ments. These were performed according to the clinical routine, without the need for consent, preoperatively and on postoperative days 1, 3, and 7 in all patients and thereafter only in those with complications until recovery or death. The following variables were considered: plasma cholesterol concentration, albumin, total protein, fibrinogen, creatinine, urate, alkaline phosphatase, γ-glutamyltransferase, total and indirect bilirubin, pro-
thrombin activity, hematocrit, hemoglobin, blood cell

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and 3 in all patients. In those recovering without complications, at postoperative day 7 cholesterol tended to return to preoperative values. In survivors who developed complications, it remained low, increasing later; in nonsurvivors it decreased further until death (Fig. 1). The trend for more severe hypcholesterolemia in these groups became significant at postoperative days 3 and 7 (Regression 1 in Fig. 1). Analysis of all postoperative measurements showed that cholesterol was correlated directly with the preoperative concentration, albumin, total protein, fibrinogen, urate, alkaline phosphatase and γ-glutamyltranspeptidase (accounting for cholestasis), prothrombin activity, hematocrit, hemoglobin, and red blood cell and platelet counts, and inversely with total and indirect bilirubin, white blood cell count, number of resected segments, and duration of operation and hepatic ischemia. Cholesterol was also lower in patients with simultaneous bowel operations, cirrhosis, and/or sepsis and in nonsurvivors. Correlations were similar in the whole sample and in subgroups of measurements ($r^2 = 0.12–0.40$; $P < 0.001$ for all). Multiple regression analysis selected the best simultaneous correlates of postoperative cholesterol that explained the maximum possible portion of its variability (Regression 2 in Fig. 1). In nonsurvivors, from postoperative day 3 onward, cholesterol and its ratio with the preoperative value were correlated directly with time to death ($r^2 = 0.60–0.85$; $P < 0.001$), but the discriminant power of single measurements in predicting outcome was poor because the pattern of death was characterized by severe and persistent decreases in cholesterol and not by isolated decreases, which also occurred in survivors. No patient in our study survived after having cholesterol <1.5 mmol/L and a postoperative/preoperative ratio <0.4 for more than 6 days.

These results show that hypcholesterolemia is not a simple expression of acute-phase response but a more complex phenomenon quantifiably related to severity of illness. Regression 2 in Fig. 1 quantifies the simultaneous impact of “adverse” factors on decreasing cholesterol. It shows that postoperative cholesterol, in addition to being related to the preoperative value, decreases with increasing magnitude of operation and decreases further if cirrhosis is present, if sepsis occurs, and with decreasing hematocrit and albumin. Indeed, each one of these factors may be associated with accelerated clearance or diminished synthesis of cholesterol-containing lipoproteins. The magnitude of the operation increases the demand for cholesterol in cell repair and new cell synthesis (9), while limiting the synthetic capability of the residual liver. This is aggravated by liver cirrhosis. Sepsis involves a stronger proinflammatory cytokine response, with a reduction in hepatic lipoprotein synthesis, a stimulation of lipoprotein receptor activity, and further impairment of liver function (4, 6, 10–12). The relationship with hematocrit involves hemodilution from blood loss, and the relationship with albumin involves the parallel impact of acute-phase response, altered synthetic adequacy of the residual liver, and hemodilution on both cholesterol and albumin. Among the adverse factors affecting cholesterol in our study, cholestasis is unique because it stimulates release of cholesterol-rich lipoprotein-X from the liver (13) and is thus expected to increase plasma cholesterol. This is consistent with the mean increase of 0.002 mmol/L per unit increase in alkaline phosphatase, as quantified in Regression 2 of Fig. 1, which is similar to that estimated in a previous study (5), and may explain the failure of patients with cholestasis to manifest extreme hypcholesterolemia.

These findings help to clarify how hypcholesterolemia in postoperative and critically ill patients becomes a cumulative index of severity of illness and its relationship with poor prognosis. The pattern of death is not characterized by low cholesterol at one single time; rather it is characterized by persistent hypcholesterolemia, as supported by separate findings showing recovery after transient postoperative decreases in cholesterol to <0.5 mmol/L followed by a steady increase (5).

Additional adverse implications of hypcholesterolemia may be related to impaired protection against proinflammatory mediators (4, 14), including impaired antioxidant capacity. As we also found, hypcholesterolemia is associated with low concentrations of albumin and urate.

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**Fig. 1.** Postoperative plasma cholesterol as a fraction of preoperative concentration (top) and results of regression analysis (bottom).

(Top) mean ± SD values are in bold; absolute values are in italics. (Bottom) regressions: postoperative plasma cholesterol (CHOL, mmol/L) as a function of preoperative concentration (PRECHOL, mmol/L), number of resected liver segments (NSEG), occurrence of complication (COMPL), death (DEATH), simultaneous bowel operations (SIMOP), presence of liver cirrhosis (CIR), sepsis (SEP), hematocrit (HCT), %, plasma albumin concentration (ALB, g/L), alkaline phosphatase concentration (ALKP, U/L; reference interval, 79–279 U/L). Regressions combine continuous and discontinuous variables. Coefficients for continuous variables (variables in parentheses) are regression slopes and estimate the mean change in postoperative cholesterol per unit change in each variable. The coefficients for discontinuous variables (variables in subscripts) are partial regression intercepts and estimate the mean decrease in postoperative cholesterol that is associated with the event indicated in the subscript; if the event does not occur, the coefficient is zero ($P < 0.001$ for whole regression and for each coefficient).

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**Regression 1:**

\[ \text{CHOL} = 0.4 \times (\text{PRECHOL}) - 0.3 \times (\text{NSEG}) - 0.6 \times (\text{COMPL}) - 0.5 \times (\text{DEATH}) + 2.1 \]

$n = 124$, measurements on days 3 and 7; $P = 0.02$

**Regression 2:**

\[ \text{CHOL} = 0.3 \times (\text{PRECHOL}) - 0.3 \times (\text{NSEG}) - 0.5 \times (\text{COMPL}) + 0.6 \times (\text{HCT}) + 0.05 \times (\text{ALB}) + 0.002 \times (\text{ALKP}) - 0.3 \]

$n = 365$, all postoperative measurements; $r^2 = 0.73$
(which account for one-half of the antioxidant capacity of plasma) (15), of vitamin E (carried in lipoproteins together with cholesterol) and other antioxidants (16), and in sepsis, with reduced antioxidant protection by sulfur amino acids (17). In sepsis, it is also related to impaired energy and amino acid disposal, which is partly reversed by increasing the amino acid supply (2,18). Recent studies also suggest that cholesterol becomes an essential substance in extreme illness (19). At present, however, the main clinical implication of severe hypocholesterolemia in acute states is the need for rapid treatment and resolution of the underlying illness.

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References
9. Chijiwa K, Kozaki N, Naito T, Okamoto S, Kuroki H Yamashita H, et al. Inactivation of the CYP21 gene may also occur through intergenic recombination with transfer of deleterious mutations from the neighboring CYP21 pseudogene. The frequency of gene deletions or conversions in CAH is controversial (3–5) and is dependent on the population studied. Evidence for gene deletions and/or conversions is traditionally obtained by Southern blot analysis. Multiple probes and separate restriction endonuclease digestions are used. TagI generates 3.7-kb (functional) and 3.2-kb (pseudogene) fragments, and 12-kb (pseudogene) fragments. These analyses have been used since 1984 (1, 3, 5–9). However, the method is indirect and time-consuming, and densitometry of fragments can be prone to error.

To identify the interchange region and improve detection of gene deletions and conversions in the RCCX module (10–13), we have developed a novel Southern blot analysis that uses two restriction endonucleases, Asel and Ndel, and requires only one probe. In addition, we use a PCR product amplified with locus-specific primers covering the TNXB gene to the 5′ end of CYP21P or CYP21P.