Plasma Fibronectin and Associated Variables in Surgical Intensive Care Patients

E. RUBLI, M.D., S. BÜSSARD, E. FREI, P. LUNDSGAARD-HANSEN, M.D., E. PAPPOVA, M.D.

An acute depletion of plasma fibronectin or FN has been observed in critically ill, surgical, or trauma patients, but there is little information on the relationships between FN levels and the final outcome in such cases, and on the simultaneous behaviour of other serum proteins. The daily values of FN, antithrombin III, IgG, C3, prealbumin, and transferrin were monitored in 98 intensive care patients after major elective surgery or trauma. According to their clinical course, they were divided retrospectively into three groups. Group A (33 patients) had sepsis. Group B (31 patients) had nonseptic complications, and group C (34 patients) had no complications in the ICU. The individual, nadir levels of FN, AT III, prealbumin, and transferrin were lower ($p < 0.01$) in the septic group A than in B and C. Within the septic group, the nadir levels of AT III, but not those of FN, were lower ($p < 0.01$) in the 14 nonsurvivors than in the 19 survivors. The FN and AT III levels had returned at least temporarily to the normal range in the six ultimate fatalities from sepsis who survived for more than two weeks. In the septic group, transferrin showed the highest percentages of actually subnormal levels and differed from FN in this respect with $p < 0.05$. Furthermore, all six proteins showed a significant overall pattern ($p < 0.01$) of parallel variations. The results confirm other reports on the behavior of fibronectin in septic patients as a group, but it was not informative as to the individual outcome, and its reduction might be viewed as part of a general plasma protein depletion associated with acute septic disease. This pattern is probably attributable to a combination of intravascular consumption and an overall excess of protein catabolism over synthesis.

From the Departments of Intensive Care and Experimental Surgery, University Hospital, Berne, Switzerland

FIBRONECTIN (FN) is a dimeric α_2-glycoprotein with a molecular weight of 440,000 Daltons and a normal plasma concentration around 300 μq/ml in man.[1,2] It is a long, thin and flexible strand with a diameter of 2 nm and a length of 120–160 nm.[3] Circumscribed domains of the molecule endow it with a number of functions currently under intensive study.[1,2] One of these, which has been explored mainly by Saba and his associates, is to stimulate the reticuloendothelial or RES clearance of particulate debris by virtue of its surface-binding properties, and thus to support the nonimmune defense of the host against different kinds of challenge.[4–6] Such challenges include burns,[7] intravascular coagulation,[8,9] experimental bacteremia and clinical sepsis,[7,10–13] starvation,[14] and surgical as well as accidental trauma.[15,16] In these circumstances, and especially in patients with proven or suspected sepsis or intravascular coagulation, the levels of immunoreactive FN are considered to represent a noninvasive index of the RES defense potential.[17]

The pattern emerging from the experiments of Saba may be summarized as follows: 1) during the acute, initial depletion of FN, the hepatic clearance of particulate matter decreases, whereas its deposition in the lungs and the kidneys is enhanced. 2) A normal RES function is quickly restored by substituting FN in a purified form or as a cryoprecipitate from fresh plasma.[18] 3) In non-substituted animals, recovery of the postinjury depletion of FN is associated with survival, whereas a persistent reduction is a harbinger of death.

These observations have aroused therapeutic interest. So far, encouraging case reports on a limited number of patients with sepsis or intravascular coagulation or both and treated with cryoprecipitates have appeared. There was evidence for at least temporary improvement of pulmonary and renal function as well as peripheral hemodynamics.[5,19–23] However, controlled studies are yet lacking, and a recent reviewer concludes that the matter is probably more complex than it appears on the experimental level.[4]

In the animal experiments, a uniform or graded, but standardized insult was inflicted upon a homogenous population. The animals received either a specific substitution or were left to their own devices, and FN was the only protein whose behavior was monitored. In clinical practice, the insult as well as the target population are markedly heterogenous, and the patients are, according to established practice, treated with nearly everything but FN. There is almost no systematically collected information either on the relationship between the clinical course and FN levels or on the associations

Reprint requests: E. Rubli, M.D., Department of Intensive Care, University Hospital, CH-3010 Berne, Switzerland.

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between FN and other laboratory data, in a substantial number of patients receiving conventional intensive care. Pott[24] reported that the FN levels of 16 patients in septic shock were significantly lower than in healthy controls, but no correlations were observed with routine laboratory parameters. Only two patients were observed for more than five days. In one, FN went downhill, and the patient died; in the other it recovered, and the patient survived. In 24 patients with severe infections or sepsis studied by Stathakis,[25] the average FN concentration was unremarkable, and no other variables were measured. Lanser[7] reported an initial depletion of FN in burned patients. Its extent parallelled the size of the injury, but it disappeared within 24 hours. A second depression occurred if sepsis supervened, in some cases prior to its clinical outset. Again, only FN was measured.

For these reasons, the plasma or serum levels of FN and five other proteins were measured in surgical intensive care unit (ICU) patients receiving no blood products enriched with respect to FN. The other proteins and the rationale for their selection were the following: Antithrombin III (AT) is a sensitive marker of intravascular coagulation[26] and bacterial infections.[27] Immunoglobulin G (IgG) and the C3 component of complement (C3) are well known participants in antibacterial defense. In addition, C3 may be depleted as one part of a "consumptive opsoninopathy" during life-threatening infections,[28] and its behavior has been recently shown to parallel that of FN during experimental sepsis in calves.[29] Transferrin (TF) and prealbumin (PA) were included since they are commonly reduced during an "acute phase reaction" because of a deficient hepatic protein synthesis[30,31] or actual hepatocellular damage.[32]

The objective was, firstly, to analyze the associations between FN, other proteins, and the clinical course of the patients including a comparison with the experimental findings. Secondly, the authors wished to see whether the behavior of FN in critically ill patients is an isolated phenomenon or part of a more general protein pattern.

Altogether, 127 patients entered this uncontrolled, screening study from January to May 1981. The first 97 cases were consecutive admissions to the surgical ICU wards. After an interim analysis of the data, another 30 patients admitted with infections were added. In the end, complete data from two or more days in the ICU were available from 98 patients, who are the basis of this report. The only reason for dropping the other 29 cases was that they were "one-day patients" only.

Methods

Laboratory Procedures

Samples of EDTA blood in polystyrene tubes and native blood in glass tubes allowed to clot spontaneously were obtained from a central venous line around 6.00 a.m. With a few exceptions, they were centrifuged within four hours for ten minutes at 3000 rev./min.

TABLE 1. *Normal Reference Values*

Protein	Unit	N	$\bar{x}$	SD	$\bar{x} \pm 2$ SD	CV*
Fibronectin	μg/ml	84	287	61	164–408	5.4
Antithrombin	mg/dl	†	23.5	3.3	17–30	5.2
IgG	mg/dl	109	831	168	495–1167	6.0
C3	mg/dl	109	124	23	78–170	3.4
Transferrin	mg/dl	117	230	50	130–330	6.2
Prealbumin	mg/dl	†	25.0	7.5	10–40	6.8

* Coefficient of variation = SD/$\bar{x}$, in per cent.
† Manufacturer's data, N unknown.

Fibronectin was assayed within 48 hours in EDTA plasma with the newly introduced Boehringer (Ridgefield, CT) turbidimetric immunoassay kit. The ten-minute extinction difference is registered with a standard photometer at 334 nm and a paper recorder, and FN is calculated in μg/ml by means of a calibration curve established with reagents included in the kit. The results of this method agree ($r = 0.92$) with those obtained with the established, but more complex electroimmunoassay.[33] The pilot studies showed that with this assay, FN is stable for 48 hours at room temperature without addition of a proteinase inhibitor, and that heparin in the concentrations found in the ICU patients (≤1 IU/ml) does not affect the results. The initial 41 assays were done in duplicate and yielded an average difference between the separate values of 4.1 ± 2.8 (SD) of the mean. For economic reasons, further work was based on single assays. In 84 healthy individuals (30 women and 54 men) aged 20 to 66 years, the authors found, as did others,[25,34] a significant correlation with $r = 0.526$, $p < 0.001$ between age and plasma FN levels. This increase with age has been speculated to reflect a functional deficiency of "senescent" FN in plasma[34] or of the cellular RES elements.[35] However, the importance of the phenomenon is unknown and there were no reference values from individuals past the age of 66, who constitute a substantial part of the ICU population. Therefore, the obtained reference values specified in Table 1 were used.

The five other proteins were assayed by established methods in the serum samples frozen at −20C for four weeks at the most after centrifugation. Antithrombin III (AT) and prealbumin (PA) assays were done by radial immunodiffusion with commercial Behringer Partigen® plates. IgG, C3 and transferrin (TF) were determined by laser nephelometry using a Hyland nephelometer and reagents.

The precision and reproducibility of all methods were monitored by including a control sample in every run

TABLE 2. *Clinical Symptomatology of 33 Septic Patients*

Spiking Temperatures	: 24 = 72.7%
Acute Respiratory Failure	: 23 = 69.7%
Shock	: 17 = 51.5%
Acute Renal Failure	: 16 = 48.5%
Hyperbilirubinemia	: 11 = 33.3%
Chills	: 8 = 24.2%
Mental Confusion	: 8 = 24.2%

and immediate checks on the results. The coefficients of variation (SD in per cent of the arithmetic mean $\bar{x}$) from ≥ 10 controls are included in Table 1, which lists the reference values of this report in a sequence adjusted to the presentation of the results.

Besides the six specific proteins, further variables such as platelet and leukocyte counts, body temperature and fluid balances were recorded according to standard practice in the ICU. They will be mentioned only insofar as they were found to be associated with the specific proteins.

Statistical Analysis

Differences between the distributions of individual values in the subgroups of patients defined under results were assessed by the nonparametric, Kolmogoroff–Smirnoff test. Where appropriate, the Chi square test was applied to a fourfold table. The relationships between the six specific proteins were evaluated by standard correlation analysis yielding the coefficient r. N denotes the number of observations. Unless specified, averages are the arithmetic mean $\bar{x}$. Variations are given as standard deviation SD. Significance levels were read from standard tables,[36] and all differences with $p < 0.05$ were considered as significant.

Results

Patient Characteristics

Of the 98 patients studied for at least two days, 27 were women and 71 were men. Their ages ranged from 18 to 81 years, with an arithmetic mean of 56 and a median of 61. To begin with, the inspection of raw FN data plots revealed that the important feature was not the basic type of injury or surgery, but the circumstances causing the admission of the patients in the ICU. For further analysis of the data, the patients were accordingly subdivided into three groups: Group A, with 33 patients, was septic. Group B, with 31 patients, had nonseptic complications, and Group C, with 34 patients, had no complications in the ICU. The age distributions of these three groups were indistinguishable, which means that the intergroup differences subsequently presented were not distorted by the relationship between age and normal FN values mentioned under methods.

In Group A with 33 patients, the clinical diagnosis of sepsis was based on a severe infection with positive local bacteriology and at least two of the clinical signs of generalization specified in Table 2.

A positive blood culture was obtained in 16 or 49% of these patients (Table 2). The authors do not, however, consider this finding to be decisive for the diagnosis of sepsis in the ICU, because their experience[37] and other reports[38,39] show that blood cultures may remain negative in patients who are, by clinical criteria, unquestionably septic. Among these patients, 19 or 58% had intra-abdominal and 14 extra-abdominal sepsis. Fourteen cases or 42% died in the ICU. Their ages ranged from 24 to 79, with a median of 63 years. In the 19 survivors, the corresponding figures were 23 to 79 and 56 years. For the group as a whole, the observation periods ranged from two to 43 days, with a median of eight.

Group B, with 31 patients, had nonseptic complications in the ICU. These were predominantly intrathoracic and infectious as well as noninfectious (*e.g.*, hematothorax). There was one case each of staphylococcal meningitis, fat embolism, and transient renal failure. One patient aged 63 died in neurologic coma. The observation periods in days ranged from two to 21, with a median of four days. Group C, with 34 patients, were postoperative or post-traumatic "surveillance" cases. The observation periods ranged from two to 12, with a median of three days. In groups B and C, fibronectin as well as the other specific proteins fell to the subnormal ranges in a number of individual patients, but an informative relationship of this laboratory pattern with the severity and evolution of their clinical condition was not discernible. For this reason, the authors used the 31 nonseptic, group B patients and the 34 uncomplicated, group C cases for comparisons with the 33 septic patients in group A.

Laboratory Profiles and Clinical Course of Septic Patients

Two typical examples of the laboratory profile and clinical course of septic cases are displayed in Figures 1 and 2. Both of these male patients entered the ICU in severe shock due to a massive, intra-abdominal infection with *E. coli*; the first survived and the second died. The figures are meant not only to illustrate those individual cases, but also to serve as a visual background for the presentation of the overall data.

To describe the general laboratory patterns of the heterogenous patient population and their relationship with the clinical course, the authors focused on the nadir and zenith levels of the six proteins attained by individual cases, and on the day-to-day oscillations of FN (Figs. 1 and 2). Since a depletion of FN is assumed to be

critical, the authors first examined the nadir levels. When compared to groups B and C, the 33 septic patients in group A showed a greater reduction of fibronectin (<0.001), antithrombin (<0.01), transferrin (<0.001), and prealbumin (<0.05), whereas no difference was found for IgG and C3. The distributions of the individual, nadir FN and AT levels in the three groups of patients are shown in Figures 3 and 4, together with the normal ranges (cf. Table 1) and subdivided according to survival or death in the ICU.

As seen from Figures 3 and 4, the patients with nonseptic complications did not differ from the uncomplicated cases. Within the septic group A, these plots furthermore reveal a dissimilarity between FN and AT: the individual nadir levels of fibronectin did not differ between the survivors and the nonsurvivors in the ICU (Fig. 3). Note also that of the four "bottom" patients with respect to FN, three survived. In the case of AT (Fig. 4), two ultimate fatalities, one Serratia sepsis and one vicious, soft-tissue infection in an immunosuppressed patient, remained in the high normal range, but the overall difference of the nadir antithrombin levels between survivors and nonsurvivors of sepsis was significant with $p < 0.01$. A "cut-off" AT level at 50% of normal revealed a striking difference of mortality: with ≥50%, it was 2/15 = 13%, *vs.* 12/18 = 67% with <50%

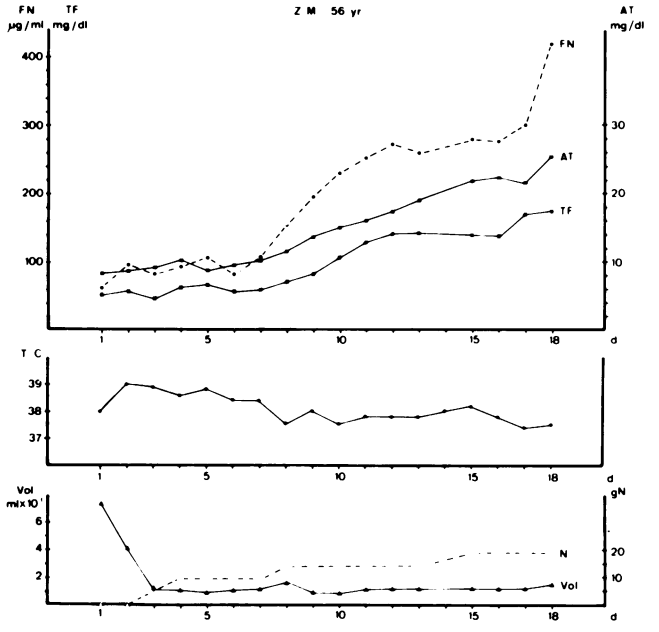

FIG. 1. Patient Z.M., 56 years. Admitted in severe shock due to intra-abdominal infection with *E. coli*. Abscissa: days following admission to ICU. Upper part: ● = Fibronectin (FN) in μg/ml, * = transferrin (TF) and ■ = antithrombin III (AT) in mg/dl. Middle part: Maximum temperature in C recorded in each 24-hour period. Lower part: ▲ = 24 hour volumes of infused fluids containing none of the proteins measured. △ = grams of nitrogen supplied per 24 hours. This patient survived.

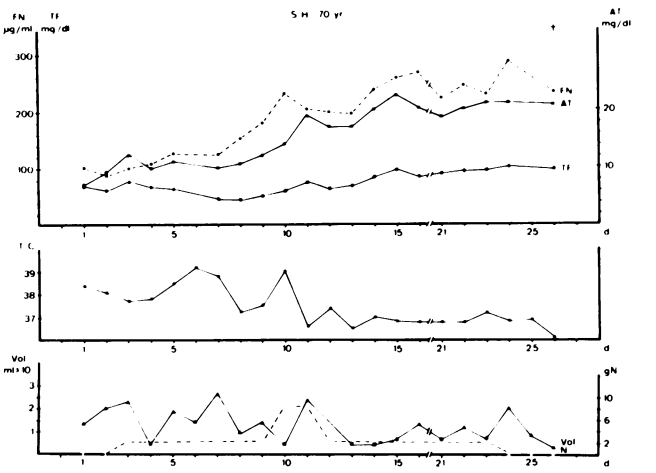

FIG. 2. Patient S.H., 70 years. Admitted in severe shock due to intra-abdominal infection with *E. coli*. Abscissa: days following admission to ICU (interruption between day 16 and 21). Display identical with Figure 1. This patient died on the 26th day.

($p < 0.01$). The predictive potential of this difference was not enhanced by combining the individual, nadir FN and AT levels to a two-dimensional plot (not shown); antithrombin remained the discriminating parameter.

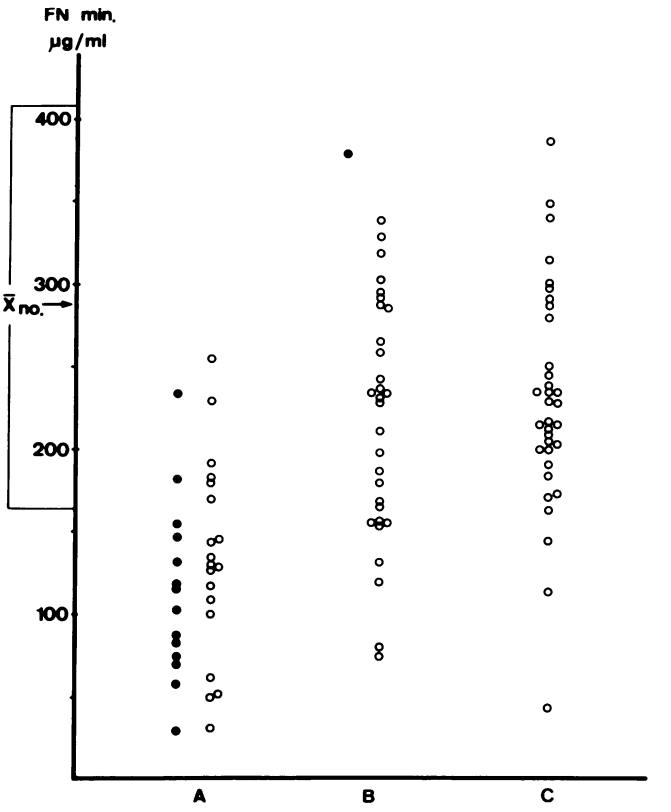

FIG. 3. Individual nadir levels of plasma fibronectin (FN), in μg/ml, in patient groups A = sepsis (N = 33), B = other complications (N = 31), and C = no complications (N = 34). Included are the normal $\bar{x} \pm 2$ SD for FN. ● = death in ICU; ○ = discharged from ICU. Differences A − B < 0.001; A − C < 0.001; B − C n.s.

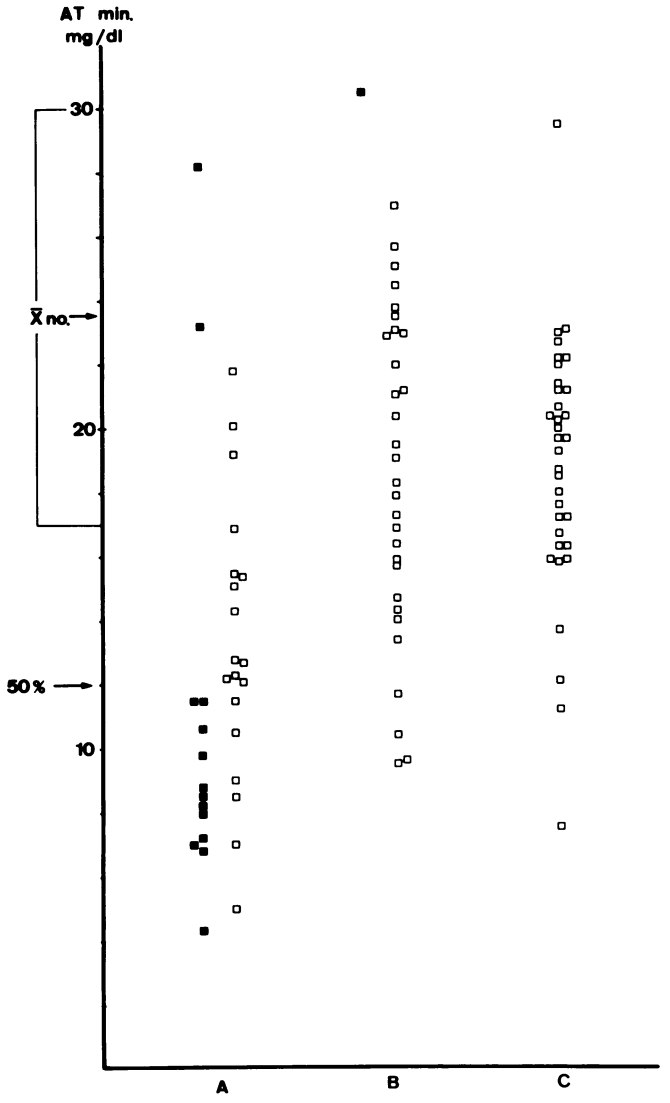

FIG. 4. Individual nadir levels of antithrombin III (AT), in mg/dl, in patient groups A, B, and C together with normal range (cf. Fig. 3). ■ = death in ICU, □ = discharged from ICU. Differences A − B < 0.01; A − C < 0.01; B − C n.s.

The individual nadir levels of FN and AT were unrelated to the survival period in the 14 ultimate fatalities, and equally unrelated to the absence or presence of positive blood cultures, with gram-positive or gram-negative organisms, organ failures, or shock. It was noted, however, that nadir C3 levels ≤60 mg/dl or about 50% of normal (Table 1) were more frequent in patients with shock than in those without (9/17 = 53% *vs.* 1/16 = 6%, $p < 0.025$). The nadir levels of the other proteins yielded no information of the kind described above.

In contrast to the nadir values, the authors found no differences of the individual zenith levels of any of the six proteins between the three groups of patients. Within the septic group, however, an individual FN zenith of 200 μg/ml, or 70% of the normal average (Table 1) suggested a distinction: with >200 μg/ml, mortality was 8/26 = 31%, *vs.* 6/7 = 86% with <200 g/ml ($p < 0.05$) The zenith AT levels gave no similar information. It is noteworthy that the individual FN and AT values had returned at least temporarily to the normal range in all of those six patients who survived for more than two weeks in the ICU, but who ultimately succumbed to refractory sepsis and/or organ failure. An example of this phenomenon was shown in Figure 2. Five of these patients were autopsied. One died of irreversible respiratory failure with extensive pulmonary destructions; his preterminal FN exceeded 300 μg/ml. Four patients had persisting, purulent intra-abdominal infections. One of these had stable FN levels >200 μg/ml. Two patients showed a preterminal decline to 100–150 μg/ml. The last patient was not monitored during his final days because the FN had risen to 340 μg/ml.

As to the day-to-day oscillations of FN, there was no patient whose clinical course enabled the authors to check the observation[7] that an abrupt drop of this protein may precede the clinical onset of sepsis. In these patients, the distributions of the 24-h oscillations of the FN levels within a range from −120 to +120 μg/ml in the three patient groups were indistinguishable, and no differences were found between the survivors and nonsurvivors of sepsis.

A General Pattern of Protein Depletion

The acute depletion of fibronectin that was observed in the 33 septic patients was not an isolated phenomenon. The individual, nadir, and zenith levels of the six proteins that were actually subnormal in these cases relative to the ranges in Table 1 are summarized in Table 3.

Transferrin showed the highest incidence of abnormal values (Table 3). In this respect, it differed with $p < 0.05$ from all the other proteins except antithrombin, whereas its nadir levels were not predictive with respect to death or recovery from sepsis. With the available 175 complete daily "profiles" of the six proteins in those patients, the authors then did a correlation analysis and obtained the highly significant ($p < 0.01$) pattern of positive associations, *i.e.*, parallel variations shown in Figure 5.

TABLE 3. *Number and Per Cent of Actually Subnormal, Individual Nadir and Zenith Protein Levels in 33 Septic Patients*

Protein	Nadir	Zenith
C3	18 = 55%	4 = 12%
IgG	22 = 67%	4 = 12%
Fibronectin	25 = 76%	3 = 9%
Prealbumin	27 = 82%	5 = 15%
Antithrombin	28 = 85%	11 = 33%
Transferrin	32 = 97%	20 = 61%

The authors considered the possibility that the infused volumes of "neutral" solutions containing none of the six proteins that were studied might have acted as a diluent influencing their serum levels (Fig. 5). The intravascular effects of the crystalloids was taken to be one third of the infused volume. As a plasma substitute, a 4% modified fluid gelatin was used, and gelatin is known to interact with FN.[40] The third neutral agent was the 4% albumin solution. The 24-hour, neutral infusion volumes as defined were recorded for the 175 daily profiles of the six proteins shown in Figure 5. They ranged from 330 to 7300 ml. No significant associations were found between these volumes and any of the protein levels. In 14 patients entering the study within 24 hours of surgery requiring total neutral infusion volumes between 500 and 6500 ml, the authors also found no associations with the protein levels of the initial sample, whereas a negative correlation with $p < 0.01$, *i.e.*, a dilution effect, was recorded with the platelet counts after 24 and 48 hours. Altogether, the protein pattern that was observed was thus not distorted by the infusion volumes administered to these patients.

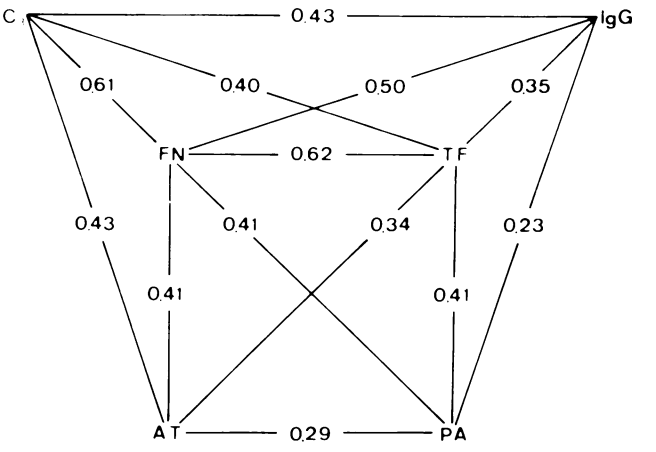

FIG. 5. Pattern of positive correlations between the protein levels in 175 data sets from 33 group A patients. r rounded to second decimal. Excepting the association IgG-PA with $p < 0.01$, all are significant with $p < 0.001$.

Discussion

The objective of this study was twofold: to examine the relationship between the fibronectin profile of non-substituted intensive care patients and their clinical course, and to see whether the—anticipated—reduction of FN in septic patients was an isolated phenomenon or part of a more general pattern of acute plasma protein depletion.

To begin with, the data confirm the tenets of Saba and his associates[5-7,9-12] insofar as septic patients, viewed as a group, do suffer a significantly greater depletion of FN than cases with nonseptic or no complications. However, this was equally true for antithrombin III, transferrin, and prealbumin. Within the septic group, the individual nadir FN levels were not predictive with respect to survival or death (Fig. 3). By contrast, the mortality was significantly higher ($p < 0.01$) in the septic patients whose immunoreactive AT levels fell to less than 50% of the normal average (Fig. 4). The "consumptive opsoninopathy" described by Alexander[28] includes a depletion of C3, and C3 levels less than about 50% of normal were significantly more frequent ($p < 0.025$) in the septic patients with shock than in those without.

The individual zenith levels of FN and the other five proteins did not differ between the three groups of patients. Within the septic group, however, mortality was lower ($p < 0.05$) in patients surpassing an FN level of 200 μg/ml, as measured with this method, whereas no similar difference was found for AT. The day-to-day oscillations of FN were unrelated to the clinical course. All of the six ultimate fatalities with sepsis who survived for more than two weeks had returned at least temporarily to the normal range of FN and AT prior to their demise. The preterminal behavior of the fibronectin levels was not uniform in those four patients who had persisting intra-abdominal infections at autopsy.

It is concluded that although the fibronectin pattern emerging from the statistical analysis of all of the 33 septic cases was, as a trend, consistent with that observed in animal experiments, the clinical setting is indeed more complex.[4] As exemplified by Figures 1 and 2, the survival of patients receiving no blood products enriched with respect to FN is neither incompatible with very low, initial levels of this protein, nor is it assured by their return to the normal range. For the individual patient receiving conventional intensive care, this study did not uncover an outstanding, monitoring or predictive value of plasma fibronectin levels.

Secondly, the acute depletion of FN in the septic patients was not an isolated phenomenon. As shown in Table 3, antithrombin III and particularly transferrin showed higher percentages of actually subnormal, nadir and zenith individual levels, with $p < 0.05$ for the difference between transferrin and FN. The highly significant pattern of parallel variations of the six proteins that were investigated (Fig. 5) does not exclude that an acute reduction of fibronectin has a pathogenic significance, with therapeutic implications, of its own, but the alternative hypothesis may be entertained that it is merely part of a general, acute plasma protein depletion associated with life-threatening, septic disease.

There are three mechanisms that might contribute to the protein pattern that was observed: intravascular consumption, a negative metabolic balance, and a "capillary

leak syndrome". FN, AT, and C3 may participate in intravascular consumptive reactions associated with sepsis and activated coagulation,[7-9,11-13,28] whereas IgG, TF, and PA do not. Transferrin showed the highest and most persistent incidence of subnormal levels (Table 3), and a depletion of this protein as well as prealbumin presumably reflects an excess of protein catabolism over the concomitant synthesis,[30-32] which is common in septic patients. In this context, it should not be forgotten that experimental starvation also depresses reticuloendothelial function by depleting fibronectin.[14] The absence of a diluting effect of the "neutral" infusion volumes on the protein levels suggests that a capillary leak syndrome was unimportant for the pattern that was observed, since these fluids were administered at the rates required to compensate for losses of intravascular volume. Other authors[7,41,42] have also recorded that capillary damage due to thermal or surgical trauma does not affect FN levels assayed in 24-hour intervals.

It is concluded that the essentially parallel depletion and recovery of fibronectin and the other five proteins in the 33 septic patients were most likely due to a combination of intravascular consumption and a general preponderance of protein catabolism over synthesis. The relative importance of these two factors almost certainly differs from case to case, and it probably also varies with time in the individual patient.

The basic remedy against both of these mechanisms is to conquer the underlying disease. The clinical effects of a specific substitution of plasma fibronectin is currently being investigated in several centers. Although the published case reports are encouraging, it is felt that these observations underscore the complexity of the circumstances and thus the necessity for carefully controlled trials.

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