3. S. G. Mamontov, M. V. Berezkin, and L. N. Ivanova, "Seasonal changes in circadian rhythms of mitosis and the response of the epithelial tissues of animals to adrenalectomy and to hydrocortisone administration," Abstract lodged with the All-Union Institute of Scientific and Technical Information, No. 3018-V86.
4. V. G. Tyshchenko, T. K. Goryshina, and V. B. Dol'nik, Problems in Space Biology [in Russian], Vol. 41, Moscow (1980), pp. 238-288.
5. J. E. Pauly, L. E. Scheving, and T. Tsai, Chronobiologiya, 4, No. 2, 177 (1977).
6. K. M. H. Philippens, H. Mayersbach, S. S. von Cardoso, et al., Chronobiologiya, 4, No. 2, 139 (1977).

MATHEMATICAL MODEL OF PROTEIN LOSS ASSOCIATED WITH PROLONGED BLOOD LOSS

B. E. Movshev and M. L. Markova

UDC 616-005.1-036.12-036.17-092.9-07:616.153.96-008.64:519.86

KEY WORDS: protein; blood loss.

For various reasons direct measurements of protein lost by the body as a result of effusion of blood or hemorrhage are not usually undertaken because it is assumed that the protein loss corresponds to the volume of lost blood. Data in the literature [6] and our own investigations [3] show that this hypothesis is more or less valid only at the beginning of blood loss. In the course of a pathological process, the protein loss is appreciably affected by changes in the hematocrit index, the concentrations of total protein and its fractions, and other factors also.

The aim of this investigation was a quantitative description of protein loss during repeated experimental effusion of blood and to predict changes in this parameter depending on the initial state of the animal and the experimental conditions.

EXPERIMENTAL METHOD

Data obtained in two series of experiments on 50 mongrel dogs were used to construct the mathematical model [3]. The experimental part of the work was described in detail previously [3, 4]. A model of prolonged blood loss [2] was created by repeated (every 15 min) bleeding from the femoral artery until the arterial blood pressure (BP) was 5.3 kP (40 mm Hg). If BP did not rise during the 15-min period, the interval between two consecutive bleedings was increased to 30, 45, or 60 min. In series I (n = 28) blood samples were taken from the animals before the experiment (under anesthesia), 1 h after the beginning of bleeding, and at the end of the phase of compensation of vascular tone, namely after spontaneous lowering of BP to 4.0-3.3 kP (30-25 mm Hg). In series II (n = 22) samples were taken before the experiment and from every portion of removed blood. The volume of removed blood was measured at each bleeding: the hematocrit index was determined at the beginning and end of the experiment and the total plasma protein concentration was measured spectrophotometrically. The protein loss during bleeding (Y, g/kg) was calculated from the results of the measurements:

$$Y = \boldsymbol{C} \cdot \boldsymbol{V} (1 - 0.96\mathrm{H}),$$

where **C** denotes the total plasma protein concentration (in g/liter), **V** the volume of blood removed (in liters/kg body weight); and H the hematocrit index (in liters/liter).

For all the portions of blood except the first to be removed, the hematocrit index was considered to be the same as that at the end of the experiment. The total protein loss after m bleedings was taken to be

Central Research Institute of Hematology and Blood Transfusion, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR O. K. Gavrilov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 104, No. 12, pp. 649-651, December, 1987. Original article submitted April 1, 1987.

 0007-4888/87/0012-1644$12.50

TABLE 1. Protein Losses (in g/kg) in Dogs during Repeated Bleedings

Series of experiments	Statistical parameter	Protein loss			
		Y_0	P_y	$P_y - Y_0$	P_y/Y_0
I (n=28)	$\bar{x}$	1,04	—	—	—
	σ	0,36	—	—	—
	v, %	34,7	—	—	—
II (n=21)	$\bar{x}$	1,22	1,78	0,56	1,49
	σ	0,37	0,45	0,23	0,25
	v, %	30,6	25,4	41,7	16,5

TABLE 2. Comparison of Observed and Calculated Values of P_y for Different Statistical Models

Model	Number of experiments, n	Residual dispersion, S^2	Mean residue $\lvert\Delta\rvert$	p
1	21	0,0522	0,198	0,01
2	21	0,0384	0,152	0,05
3	21	0,0319	0,153	0,05
4	21	0,0346	0,153	0,001
4	34*	0,0390	0,159	0,01

Legend. *) Thirteen experiments from series I are included.

$$P_y = \sum_{i=0}^{m} Y_i \; (i = 0.1.2,..,m),$$

where i is the serial number of the bleeding. The data were subjected to statistical analysis by parametric tests [5]. The adequacy of the mathematical models was tested on the Iskra-226 computer. The aim of the analysis was to determine the value of P_y and its dependence on the number of bleedings and the duration of the phase of BP compensation.

EXPERIMENTAL RESULTS

The statistical robustness of the values obtained for initial and total protein loss increased in the order $Y_0 - P_y - P_y/Y_0$ (Table 1). This indicates correlation between the initial and total protein losses. This dependence can be expressed quantitatively by model 1:

$$P_y = 1.022Y_0 + 0.531. \quad (1)$$

The coefficients were calculated by the method of least squares. Adequacy and significance of the regression model were tested by methods of dispersion and correlation analysis [1]. The factor characteristic accounts for 80.7% of the regression. The relationship between Y_0 and P_y is linear ($r = 0.856$) and significant ($p < 0.01$). The model adequately describes the empirical data of the experiments of series II (Table 2).

Dependence of the protein loss on the duration of the experiment (t, in h) is described by model 2:

$$P_y(t) = Y_0 + 0.655\left(1 - e^{-t}\right), \quad (2)$$

and dependence on the number of bleedings by model 3:

$$P_y(m) = Y_0 + 0.85e^{-1.7/m} \quad (3)$$

where e is the base of natural logarithms and m the number of bleedings, excluding the first. Models 2 and 3 reflect the exponential rise of protein losses in the course of the experiment (Fig. 1). The best matching between the empirical and calculated data was obtained for $t < 1.5$ h and $m \leq 6$. This can be explained by the large number of observations in the early stages and the considerable variability of the results in dogs with long-term compensation of vascular tone.

The coefficients of models 2 and 3 were calculated with respect to the mean value of protein losses in the set. Testing the adequacy of the models by using the value of the residues (difference between observation and prediction) revealed no clear anomalies, no appreciable changes of dispersion or sequences with a regular character. Dependence of the residues on Y_0, t, and m was not found. Models 2 and 3, unlike model 1, adequately describe the change in magnitude of the losses in the course of repeated bleedings. The limiting value of the protein losses under the experimental conditions can be estimated by both these models. If it is assumed that $Y_0 = 1$, the value of P_y will tend toward the limit $\lim P_y = (1.54 \pm 0.32)$. This evidently corresponds to exhaustion of the compensatory powers maintaining vascular tone.

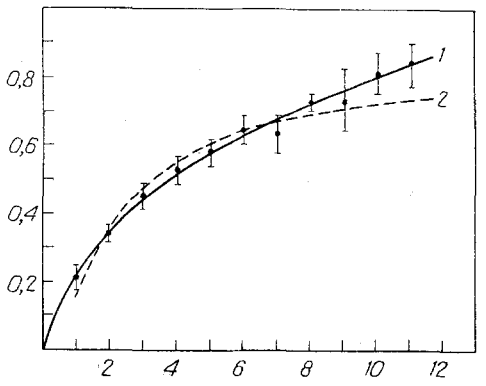

Fig. 1. Increase in protein loss depending on number of repeated bleedings of dogs. Abscissa, number of bleedings; ordinate, quantity of protein lost, disregarding losses with initial bleeding (ΣI_i, g/kg). 1) Results of observations ($\bar{x} \pm m$); 2) calculated data using model 3.

The decrease in the quantity of protein lost by the body with each successive bleeding is linear in character and can be described by model 4:

$$P_y = Y_0 + \sum_{i=1}^{m} Y_i$$
$$-\ln Y_i = 0.389i + 1.187, \quad (4)$$

where i denotes the serial number of the bleeding, disregarding the first. The point estimates of the parameters were calculated by the method of least squares in each experiment and were averaged with weights inversely proportional to dispersions of the regression line. In addition to methods of testing adequacy used previously, model 4 was compared for all measurements of series II and for two measurements of series I (1 h after the beginning of bleeding and at the end of the experiments). Satisfactory agreement between the empirical and calculated data confirms the adequacy of model 4. No significant relationship could be found between the coefficients of the model and the duration of the phase of BP compensation or the total number of bleedings. Thus models 1-4 as a whole adequately reflect protein losses during repeated bleedings. Estimates of P_y suitable for practical purposes can be obtained by measuring only one value of Y_0, with subsequent calculation in accordance with model 1. If the total number of bleedings and (or) the duration of the phase of BP compensation are known, models 2 and 3 are more efficient. With a large number of bleedings (in animals with well marked compensation of BP), the data can be described most accurately by model 4. Besides, with model 4 suggestions can be put forward regarding the internal mechanism determining the magnitude of the protein loss. The second term in model 4 is a sum of values from which each successive one is proportional to the quantity of protein remaining in circulation. Dependences of this kind can be satisfactorily described by differential equations of the first order, and they are often used to characterize the reserves.

It can be tentatively suggested that the two-component nature of the models corresponds to two factors determining the magnitude of protein loss and its variation from individual to individual. The more variable value Y_0 depends on individual differences of the vascular tone mechanism. The more stable value ΣY_i characterizes the protein reserves and the processes of their mobilization. Dependence of total protein losses on the initial state of the animal is evidently expressed through the parameter Y_0, and dependence on the experimental conditions by Y_i.

The mathematical models suggested are suitable for estimating the protein balance, calculating plasma protein reserves, and determining the trend of the transfer of protein into the blood stream in cases of acute blood loss and hemorrhagic shock. The protein loss model may find an application in the development of programs for transfusion therapy of extremal states.

LITERATURE CITED

1. N. R. Draper and H. Smith, Applied Regression Analysis, New York (1966).
2. N. I. Kochetygov, Plasma Expanders in Blood Loss and Shock [in Russian], Leningrad (1984), pp. 32-39.
3. B. E. Movshev, G. N. Kurbanova, Yu. A. Litvinenko, and M. L. Markova, Patol. Fiziol., No. 6, 67 (1986).
4. B. E. Movshev, M. L. Markova, G. N. Kurbanova, et al., Current Problems in the Pathogenesis and Treatment of Acute Blood Loss [in Russian], Moscow (1986), pp. 41-43.
5. J. H. Pollard, A Handbook of Numerical and Statistical Techniques, New York (1977).
6. L. C. Getzen, E. W. Pollak, and E. Wolfman, Surg. Gynec. Obstet., 133, No. 1, 42 (1977).