only 24 h before alcohol was discontinued. Anti-BSA antibodies had no effect on the manifestation of withdrawal. Our experiments demonstrated that antiserotonin antibodies alleviate the manifestations of withdrawal syndrome in mice when injected 24 h before or after alcohol is discontinued. The efficacy is higher in the former case. The weakly pronounced immunomodulating antiwithdrawal effect of rabbit γ-globulin may be related to the presence of normal antibodies to serotonin. The inefficacy of anti-BSA antibodies is in line with the results of their administration with the aim of eliminating alcohol motivation [2]. On the whole, our results confirm the data of our previous research, in which the possibility of passive immunization with antibodies to serotonin for the treatment of alcoholism was demonstrated [3,4].

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Blood Rheology in Experimental Diabetes Mellitus

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One of the major causes of unsuccessful prevention and treatment of diabetic angiopathies is lack of knowledge about the mechanisms of their development [1,11].

The objective of the present study was to explore the membrane disturbances in the formed elements of the blood and their effect on the blood rheology in the early stages of experimental diabetes mellitus.

MATERIALS AND METHODS

The experiments were carried out on male albino rats. A model of type I diabetes mellitus was created by administering a 5% solution of alloxan hydrate (Chemapol, Czechoslovakia) in a dose of 11 mg/100 g, i.p. The severity of diabetes was judged by the blood sugar level, which was assayed by the orthotoluidine method. The assays were performed on days 7 and 14 of the experiment. The electrical breakdown of the erythrocyte membrane, the electrophoretic mobility and ξ-potential of the erythrocyte membrane, the shear velocity, and the dynamic viscosity of the blood were determined. The electrical breakdown of the erythrocyte membrane was determined after Putvinskii [4] by placing erythrocytes in media with low concentrations of Cl^-. The electrophoretic mobility and ξ-potential were determined by Stolyar's micromethod [6]. The ξ-potential of the erythrocyte membrane was calculated by the formula:

$$\xi = \frac{4\pi U}{HD},$$

where U is the erythrocyte mobility; H is the potential gradient; D is the dielectric constant of the medium; and 4π is a coefficient. The vis-

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cosity was determined using modified techniques of Udovichenko [5]. The viscosity indexes were determined as the shear velocities at the following values of pressure delivered to the capillary from a preostat: 2, 4, 8, 12, and 16 mm water column. The results were calculated by the following formula:

$$\eta = \frac{100 \cdot g \cdot r^4}{8 \cdot R^2 \cdot l},$$

where R is the radius of the wide portion of the capillary; r is the radius of the narrow portion; l is the length of the narrow portion; t is the time of movement; p is the pressure delivered to the capillary from a preostat; g is the acceleration of gravity (980 cm/sec).

RESULTS

The blood rheology is largely determined by the behavior of the erythrocytes, since they are usually the major cellular elements in the suspension.

In our studies of the electrical breakdown of the erythrocyte membrane the potential constituted 76.2±0.39 mV; on the 7th day this parameter was 98.7±0.46 mV, which was 29.5% higher than in the control group. On the 14th day we observed an exacerbation of the process, which manifested itself as an increased value of electrical breakdown of the erythrocyte membrane to 113.4±0.74 mV (48.8% higher than in the control group).

These data, in our opinion, attest to a reduced selective permeability of the erythrocyte membrane during the course of experimental diabetes, leading to a disturbance of both the passive and active transport of substances via the cell membrane, which still further aggravates the tissue hypoxia developing in diabetes mellitus [2,3].

In the control group of animals the ξ-potential was 19.2±0.12 mV. Our studies showed that on day 7 this parameter dropped to 17.3±0.09 mV, this being 9.5% lower than in the control, and on day 14 this drop was as much as 30.9%, and the potential constituted 13.2±0.08 mV.

Such erythrocytes with a reduced electrical charge come in contact with each other as they travel along the capillaries. As a result, their aggregation and adhesion occurs, and this inevitably causes changes in the blood viscoelasticity [8,10].

Studies of the blood viscosity in the control group of animals showed that at a temperature of 37°C the viscosity was 5.1±0.006 and 2.8±0.02 cP for a pressure of 2 and 16 mm water column, respectively. As soon as on day 7 a pronounced increase of the blood viscosity was shown for low shear velocities. For example, at 2 cm water column the blood viscosity for a shear velocity of 9.61±0.63 sec^{-1} was 8.2±0.04 cP, this being 60.7% higher than this index in the control group. The same parameter at higher shear velocities was 3.85±0.03 cP (37.5% higher than in the control). On day 14 we observed an aggravation of these changes, which was primarily manifested as an increased shear stress (up to 4 mm water column). The viscosity at a minimum shear stress was 88.2% higher than that in the control group and constituted 9.6±0.05 cP. For a pressure of 16 mm water column the blood viscosity at a shear velocity of 18.52±1.47 sec^{-1} was 5.1±0.8 cP (Fig. 1).

We regard these changes as a logical result of the membrane disorders associated with a loss of electrical stability.

Our findings provide a basis for the conclusion that changes in the cell membrane, manifesting themselves in the earliest stages of diabetes mellitus, initially give rise to functional disturbances such as a reduced shear velocity of the blood and an increase in its viscosity. A reduced blood flow rate and hyperglycemia-induced serum proteins cause aggregation and adhesion of the formed elements of the blood along with vessel obturation. Early on, this leads to an increase of the hydrostatic pressure in the microcirculatory bed. together with a disturbance in the vasomotor sensitivity and the subsequent development of generalized vasodilation [7,9]. An increased capillary pressure and an elevated level of glycosylated hemoglobin promote an increase in the permeability of the capillary walls, as well as the development

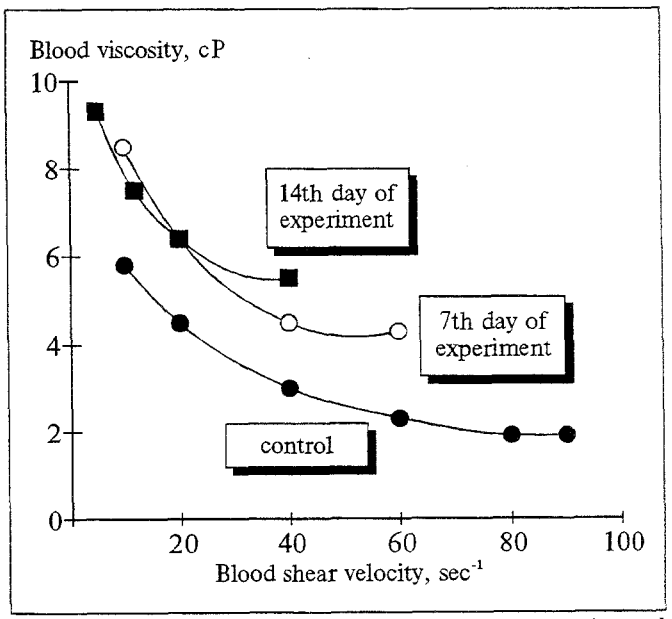

Fig. 1. Dynamic viscosity of blood in rats with experimental alloxan diabetes.

of tissue hypoxia. In addition to their direct impact on the microvessels, the ongoing action of these factors promotes plasma penetration in the basal membrane and provokes proliferation of the vascular endothelium by raising the permeability of the capillary walls for diverse types of macromolecules, this inevitably leading to occlusion of the vessel lumen and to exacerbation of the primary disturbances. Thus, the chain of pathological reactions is closed, and a vicious circle is formed. Under such conditions, correction of metabolic disturbances alone is unable to break this state, since the chain is closed by the damage to the membrane structures, and these disturbances may also aggravate each other in the absence of metabolic disorders.

Hence, diabetic microangiopathies are to be regarded as a manifestation of diabetes mellitus of a polypathogenetic nature.

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Antiepileptic Effects of Glutapyrone, a Novel Derivative of 1,4-Dihydropyridine, Administered in Combination with Sodium Valproate and Phenobarbital

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The leading trend in modern pharmacotherapy is a combined administration of drugs, which makes it possible to use the potentiation phenomenon and to act simultaneously upon a number of elements of the pathological process [1,5-9]. Although glutapyrone is a derivative of the 1,4-dihydropyridines (DHP), in contrast to classical 1,4-DHP, it has previously been shown not to affect the $^{45}Ca^{2+}$ uptake by rat brain synaptosomes or the hemodynamics [2,11]. At the same time, the profiles of anticonvulsive activity of

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