3. F. C. Sauer, J. Comp. Neurol., 63, 13 (1935).
4. B. M. Patten, Human Embryology, New York (1953).
5. J. Langman, Medical Embryology, Baltimore (1963).
6. L. B. Arey, Developmental Anatomy, Philadelphia (1965).
7. L. Puelles and A. Privat, Anat. Embryol., 150, 187 (1977).
8. S. Puszkin, S. Berl, E. Puszkin, et al., Science, 161, 170 (1968).
9. R. E. Fine and D. Bray, Nature, 234, 115 (1971).
10. S. Puszkin, W. J. Nicklas, and S. Berl, J. Neurochem., 19, 1319 (1972).
11. S. Berl, S. Puszkin, and W. J. Nicklas, Science, 179, 441 (1973).
12. A. A. Milokhin, S. S. Reshetnikov, and I. V. Chernova, Byull. Éksp. Biol. Med., No. 3, 368 (1978).

MICROCIRCULATION IN THE SEROUS MEMBRANES OF RATS WITH SPONTANEOUS GENETIC HYPERTENSION

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A comparative study was made of the microcirculation (MC) of the serous membranes of rats with spontaneous genetic hypertension (SHR) and rats with normal blood pressure (Wistar). The disturbance of MC in hypertension was shown to affect the system as a whole, as shown by structural changes in each of its components (arterioles, precapillaries, capillaries, postcapillaries, venules, lymphatic capillaries and postcapillaries, nerve fibers), and the lesions were generalized, for the changes in all serous membranes studied were of the same kind. The similarity of the changes in MC of the serous membranes of SHR rats and of persons dying from essential hypertension confirms the hypothesis that the changes in MC are stereotyped and relatively specific for hypertension. The specificity of the hypertensive changes in MC is expressed as severe vascular changes of a special kind, whereas the nonspecific changes consist of a combination of intra- and perivascular changes accompanied by only minimal vascular changes, representing the universal response of MC to various stresses.

KEY WORDS: microcirculation; spontaneous genetic hypertension; essential hypertension.

Progress in the study of structural and functional organization of the microcirculation (MC) under normal and pathological conditions has necessitated the compiling of a nosological classification of its changes [7]. Two types of responses of the microvessels have been postulated: 1) stereotyped, observed in various pathological states, and 2) relatively specific for each disease, indicating that the disease leaves a functional and morphological imprint on all structures of MC [5, 6]. To detect specific changes in the microvessels both in the patient during life and in autopsy material, the investigator must make allowance for various additional conditions: age and the presence of atherosclerosis, complications of the underlying disease, and accompanying diseases and their complications [10, 11]. The influence of these conditions on the character of the changes in MC can be excluded by creating an experimental model of the disease. The most adequate model of essential hypertension in man is spontaneous genetic hypertension in rats of the SHR (spontaneously hypertensive rats) line [4, 15].

The object of this investigation was to study the MC of serous membranes in rats of this line in order to distinguish changes due to hypertension and to confirm the concept that stereotyped and relatively specific responses of the microvessels may take place in this disease.

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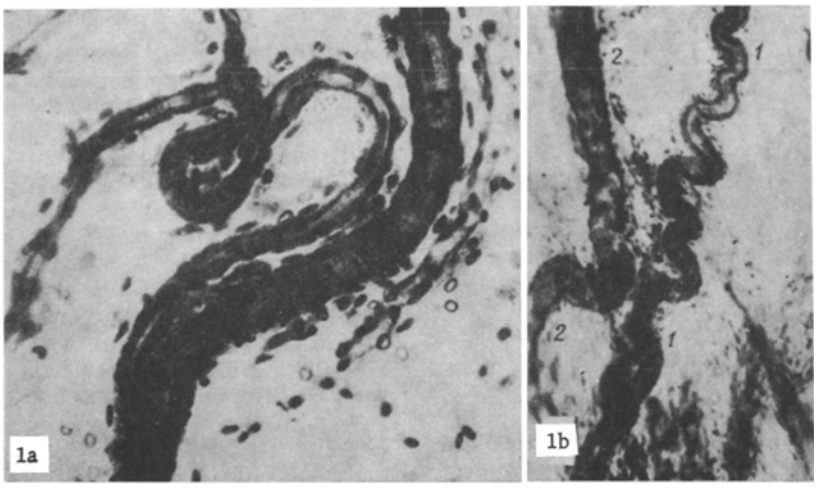


Fig. 1. Capsule of the kidney: a) twisted arteriole and precapillary (250 ×); b) twisted arteriole (1), deformed venule (2), (120 ×). Here and in Figs. 2 and 3, impregnation with silver nitrate by Kupriyanov's method.

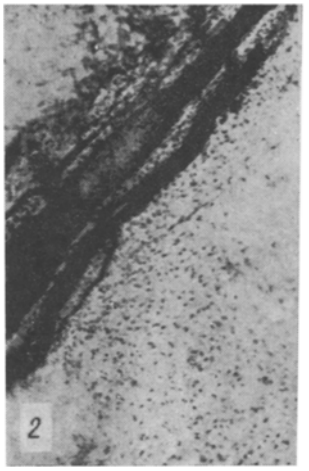
EXPERIMENTAL METHOD

Experiments were carried out on nine inbred male SHR rats aged 12-14 weeks, weighing 209.9 ± 6.1 g, and with an arterial pressure of 175.0 ± 4.3 mm Hg. Eleven inbred male Wistar rats of the same age, weighing 218.6 ± 8.4 g, and with an arterial pressure of 93.3 ± 4.0 mm Hg, served as the control. To isolate the serous membranes (kidney capsule, mesentery,

TABLE 1. Scale of Evaluation of Changes in MC, in Points

Changes	Features \ Vascular components of MC	Arterioles	Precapillaries	Capillaries	Postcapillaries	Venules	Maximal total number of points
Vascular	Irregularity of caliber						
	a) in localized segments	1	1	1	1	1	
	b) along whole length of vessel	2	2	2	2	2	10
	Deformation of vessel walls						
	a) unilateral swellings and invaginations (without microaneurysms)	1	1	1	1		
	b) bilateral swellings, folding, single microaneurysms	2	2	2	2	2	20
	c) multiple microaneurysms	3	3	3	3	3	
	d) polymorphic deformations, saturation	4	4	4	4	4	
	Tortuosity of vessels						
	a) single smooth waves	1	1	1	1	1	
	b) focal (without twists)	2	2	2	2	2	
	c) total (without twists)	3	3	3	3	3	
	b) Twists, loops, tangles	4	4	4	4	4	20
							Total 50 points
Arteriolo-venular anastomoses	a) single			1			
	b) multiple			2			2
Intravascular changes	a) sludge phenomenon	1	1	1	1	1	
	b) microthrombi	2	2	2	2	2	10
Extravascular changes	Perivascular edema			1			
	Hemorrhages			2			2
Changes in lymphatic components of MC	Lacunar dilatation of lymphatic capillaries and postcapillaries			1			
	Dystrophic changes			1			3
	Sclerotic changes			1			
Changes in nerves	Separation of fibers			1			
	Thickenings						
	a) single			1			3
	b) multiple			2			

Over-all maximal index of changes in MC 70 points



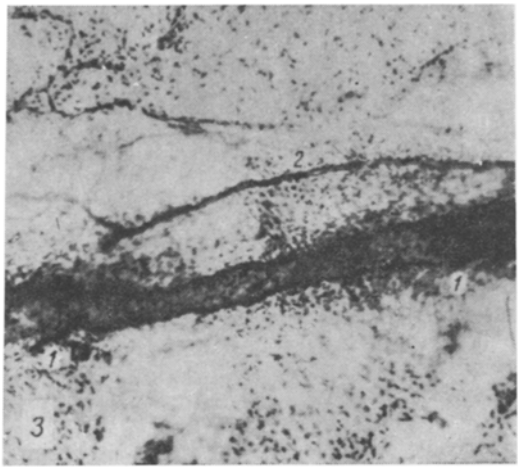


Fig. 2 Fig. 3

Fig. 2. Mesentery of small intestine: cylindrical aneurysm in arteriole (75 ×).

Fig. 3. Capsule of kidney: considerable deformation of venule (1), narrow precapillary (2), (75 ×).

peritoneum, pericardium, parietal pleura) thoracotomy and laparotomy were performed on all the animals. The extensive traumatic operation and massive blood loss led to the development of shock in the animals before death. The serous membranes were fixed in 12% neutral formalin, then spread out into very thin films and impregnated with silver nitrate by Kupriyanov's method.* The film preparations were studied in the light microscope. Changes in MC were assessed in points on the writer's scale (Table 1) and the volume density of MC and diameters of the microvessels were determined, with appropriate statistical analysis of the data [1].

EXPERIMENTAL RESULTS

The study of film preparations showed that changes in MC in all the serous membranes studied were similar in type in the rats of each group; accordingly, a combined description will be given of the changes in MC as they affect its various components.

In the serous membrane of Wistar rats the arterioles and precapillaries were straight, with slight variations in the width of the lumen, and the precapillary sphincters were closed. Most of the capillaries were in a collapsed state, short segments followed an undulating course, and deformation of their walls was minimal. The postcapillaries and venules were dilated, with more marked variations in the width of the lumen, twisting, and deformation of the walls as unilateral swellings and folding. Within the lumen of the microvessels aggregates of erythrocytes and microthrombi were found. These changes in MC were identical with those described previously in the serous membranes of persons dying accidentally [2].

In MC of the serous membrane of SHR rats more marked and varied deformations of the walls of all the microvessels were observed: folding, bilateral multiple swellings and invaginations, microaneurysms, and sacculations; considerable twisting (especially of the arterioles and precapillaries) with the formation of loops and tangles, and variation in the caliber of the vessels along their whole length (Figs. 1-3). Changes in MC of a similar character also were found by the writer in the serous membranes of persons dying from essential hypertension [2].

Analysis of the results of the quantitative investigation of the state of MC in points showed no significant difference between the indices of the intra- and extravascular changes or the presence of arteriolo-venular anastomoses in the MC of the SHR and Wistar rats. This

*These experiments were carried out in the Morphological Laboratory (Director, Professor Yu. V. Postnov) Fourth Main Board, Ministry of Health of the USSR. The author is grateful to Professor Postnov for providing the material for this investigation.

confirms the suggestion that aggregation of erythrocytes, the formation of microthrombi, the increase in permeability of the walls of the microvessels with the development of perivascular edema and hemorrhages, and the opening of most of the arteriolo-venular anastomoses are stereotyped reactions of MC characteristic of extremal states [6, 8]. In SHR rats, statistically significantly higher values of the over-all index of changes in MC (46.6 ± 2.1 points) and in the index of vascular changes (34.6 ± 1.9 points) compared with the control animals (32.2 ± 1.3 points and 21.3 ± 1.4 points; $P < 0.05$) were found. Consequently, the relative specificity of the changes in MC in hypertension are expressed as a much higher level of the vascular changes in its components. The diameters of the arterioles and precapillaries are smaller ($P < 0.05$) in SHR rats but the diameters of the venules and postcapillaries are larger ($P < 0.05$) than in Wistar rats. The diameters of the capillaries in these animals do not differ significantly ($P > 0.05$). Some workers [9, 12, 13] observed an increase in the pressor vascular response in patients with essential hypertension and also in animals with experimental hypertension. This could evidently account for the more marked constriction of the arterioles and precapillaries in SHR rats under the influence of vasoactive metabolites accumulating during shock [8]. The increase in the diameters of the postcapillaries and venules was possibly connected with the marked deformation of their walls which took place throughout the extent of the vessels. A stereometric study of the volume density of MC showed a statistically significant increase in this index in hypertension.

Only slight dystrophic changes, namely focal separation of endothelial cells and vacuolation of their cytoplasm, were observed in the walls of the lymphatic microvessels of the Wistar rats, whereas in the SHR rats marked dystrophic and sclerotic changes were found. The volume density of the lymphatic capillaries and postcapillaries was significantly higher in hypertension than when the blood pressure was normal ($P < 0.05$). This could be due to an increase in their number and their diameter and is evidence of an increased functional load on the lymphatic component of MC when changes affect the blood vascular components in hypertension [3, 14].

In the SHR rats a statistically significant increase was found in indices reflecting changes in the nerves, compared with the control Wistar rats. This increase could reflect disturbances in the innervation of the microvessels associated with the pathogenetic mechanisms of this disease.

Investigation of changes in MC of serous membranes in SHR rats thus revealed 1) that the lesions in MC are systemic in character, as shown by structural changes in each of its components, 2) that the lesions of MC are generalized, as shown by the uniform changes in the microvessels in all the serous membranes studied, and 3) that these changes are similar with the changes in MC in persons dying from essential hypertension. The results thus confirm the hypothesis that changes in MC may be either stereotyped or relatively specific for hypertension.

LITERATURE CITED

1. G. G. Avtandilov, Morphometry in Pathology [in Russian], Moscow (1973).
2. A. A. Vorob'eva, Arkh. Patol., No. 1, 22 (1978).
3. V. P. Kaznacheev and A. A. Dzizinskii, Clinical Pathology on Transcapillary Exchange [in Russian], Moscow (1975).
4. Yu. V. Postnov, S. N. Orlov, and A. S. Shevchenko, Kardiologiya, No. 10, 88 (1975).
5. A. I. Strukov, R. A. Simakova, and T. G. Khlebnikova, Arkh. Patol., No. 9, 22 (1975).
6. A. I. Strukov and A. A. Vorob'eva, Kardiologiya, No. 11, 8 (1976).
7. A. M. Chernukh, in: Problems in the Microcirculation (Abstracts of Proceedings of the 2nd All-Union Conference) [in Russian], Moscow (1977), p. 5.
8. A. M. Chernukh, P. N. Aleksandrov, and O. V. Alekseev, The Microcirculation [in Russian], Moscow (1975).
9. E. Davis and J. Landau, Biol. Anat. (Basel), 9, 1 (1967).
10. F. Elliott and S. Leonberg, Am. J. Med., 63, 208 (1977).
11. N. Heisig, Arch. Kreisl.-Forsch., 47, 95 (1965).
12. R. E. Lee and E. A. Holze, J. Clin. Invest., 30, 539 (1951).
13. L. Illig, Die Terminale Strombahn, Berlin (1961).
14. N. Sukriti, D. M. Robertson, and H. B. Dinsdale, Lab. Invest., 36, 150 (1977).
15. Y. Yamori, Jpn. Circulat. J., 41 (1977).