tains up to 80% of the total blood histamine, and this has been confirmed by one of us.[5] It may be that during anaphylactic shock, such histamine is liberated into the plasma where it is free to exert its effect, and from which it is rapidly removed by various tissues, such as occurs in the rat (Rose and Browne[6]) or that the rapid disappearance is coincident with the sudden withdrawal of white blood cells from the circulation during anaphylactic shock in the rabbit. It should be noted that there is no correlation between the severity of the symptoms and degree of change in the histamine content of the blood as observed in these preliminary experiments. The relationship of the cortin to anaphylaxis will be discussed elsewhere.

Summary. During acute anaphylactic shock in the rabbit, a marked decrease in total blood histamine occurs. No increase of plasma histamine is observed.

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Effect of Cyanide on Cerebral Metabolism.*

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Loevenhart[1] suggested the use of small doses of cyanide intravenously in the treatment of schizophrenia. Since many methods now employed for treating schizophrenia (metrazol,[2] insulin,[3] and nitrogen[4]) depress cerebral metabolism the present study was made to determine the effect of small concentrations of cyanide on cerebral metabolism *in vivo*. In addition a comparison was made between the effects of intravenous cyanide on cerebral and muscular metabolism.

Method. Dogs were anesthetized with pentobarbital and the superior longitudinal sinus, femoral vein and artery were exposed. Blood was drawn before and for various periods after the intra-

[5] Rose, B., unpublished results.

[6] Rose, B., and Browne, J. S. L., *Am. J. Phys.*, 1938, **124**, 412.

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[1] Loevenhart, A. S., Lorenz, W. F., Martin, H. G., and Malone, J. F., *Arch. Int. Med.*, 1918, **21**, 109.

[2] von Meduna, L., *Z. f. g. ges. Neur. u. Psychiat.*, 1935, **152**, 235.

[3] Sakel, M., *Nerv. and Ment. Dis.*, Monograph No. 62, New York, 1937.

[4] Himwich, H. E., Alexander, F. A. D., and Lipetz, Basile, PROC. SOC. EXP. BIOL. AND MED., 1938, **39**, 367.

venous injection of potassium cyanide. The blood samples were then analyzed for oxygen.[5] The difference in oxygen contents of the femoral artery and superior longitudinal sinus represent the cerebral oxygen consumption, chiefly of the cerebral cortex; the differences between femoral artery and vein and the oxygen uptake of muscle.

Results. Thirty-seven observations were made on 11 dogs and typical results are presented. Table I reveals the effects on cerebral metabolism of a large dose of potassium cyanide injected into the common carotid artery. A severe and prolonged depression of oxygen uptake is observed and is still greatly reduced 1½ hours after the injection. In Table II are seen the effects of a small injection followed by a larger dose of potassium cyanide, both injected into the femoral vein. The larger amount produced a more profound depression of oxygen utilization. A dose of cyanide which inhibits

TABLE I.
Effect of Potassium Cyanide on Cerebral Respiration.

Vol. % of Oxygen				
Arterial	Venous	Differences	Time and Amount	Remarks
15.93	7.02	8.91	3 min before KCN	KCN injected into carotid artery
16.92	16.34	.58	2 min after 20 mg KCN	
16.37	15.67	.70	18 min after injection	
15.67	10.96	4.71	1 hr 32 min after injection	

TABLE II.
Effect of Potassium Cyanide on Oxygen Uptake of Brain.

Vol. % of Oxygen				
Arterial	Venous	Differences	Time and Amount	Remarks
14.38	9.12	5.26	Before KCN	KCN injected into femoral vein
12.09	9.85	2.24	7 min after 5 mg KCN	
14.86	8.11	6.75	1 hr after KCN	
15.89	14.56	1.33	10 min after 15 mg KCN	

TABLE III.
Effect of Potassium Cyanide on Brain and Muscle.

Vol. % of Oxygen				
Arterial	Venous	Differences	Time and Amount	Remarks
15.20	B 9.69	B 5.51	7 min before KCN	KCN injected into femoral vein
	M 5.95	M 9.25		
16.83	B 14.33	B 2.50	After 5 mg KCN	
	M 6.15	M 9.68		
15.72	B 11.68	B 4.04	7 min after injection KCN	
	M 4.94	M 10.68		

[5] Van Slyke, D. D., and Neill, J. M., *J. Biol. Chem.*, 1924, **61**, 523.

markedly brain metabolism is without apparent effect on muscle (Table III).

From the results it may be seen that cyanide in various concentrations inhibits cerebral metabolism *in vivo*. If a suitable concentration is administered a depression equal to or greater than that resulting from either metrazol or insulin or nitrogen may be obtained. The underlying mechanism with each agent, however, is different. With metrazol the cause of the cerebral metabolism may be attributed to an arrest of respiratory movements due to severe convulsions. Blood, therefore, passes through the lungs in an unoxygenated form and the brain is deprived of its oxygen supply. In the case of insulin hypoglycemia the diminished concentration of sugar, the chief substrate of the brain, is the underlying factor for the depression of cerebral metabolism. In the nitrogen therapy the decreased cerebral oxygen uptake is due to the replacement of oxygen by nitrogen in the inspired air. With cyanide, on the other hand, a direct poisoning of the enzyme oxidase prevents the combination of the substrate with oxygen. Thus, we see that all treatments thus far used for schizophrenia diminish in one manner or another cerebral oxidations.

Since a large concentration of cyanide causes a marked inhibition of cerebral respiration *in vivo*, it may be concluded that a cyanide-sensitive system may account for the greatest part of cerebral respiration.

It is surprising to note that concentrations of cyanide which inhibit cerebral respiration nevertheless exert no significant decrease on the oxygen consumption of muscle. Several explanations may be ventured. It is possible that qualitatively a smaller reserve of the cyanide-sensitive oxidase enzyme is available in the brain. Thus for the same concentration of cyanide a greater proportion remains in active form in muscle. It is not likely that the cyanide fails to penetrate muscle nor that changes of blood flow different in muscle and brain can explain the differential effect on these two tissues.

Summary and Conclusions. The effects of intravenous and intracarotid cyanide injection on cerebral and muscle metabolism were studied; 37 observations were made on 11 dogs. A significant decrease in the cerebral oxygen consumption was observed, a decrease which varied directly with the concentration of cyanide used. The concentration of cyanide which depressed metabolism of brain failed to exert an effect on the arterial-venous difference of muscle blood. The significance of these findings is discussed.