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Physiological Studies of Rhenium Compounds.

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A study of the behavior of potassium perrhenate in mice and rabbits[1] indicated that the element rhenium was not very toxic in the animal body. The low solubility of the $KReO_4$ often demanded injections of such large volumes that they exceeded the capacity of the animals. Since that time the more soluble salt $NaReO_4$ has been prepared. A study of some of its action in the animal body follows:

Toxicity in Rats. A $NaReO_4$ solution containing 42 mg of Re per cc of solution was injected intraperitoneally into 11 immature female rats weighing 58-71 g; the largest volume injected did not exceed 2.0 cc of solution. Six rats receiving 310, 350, 545, 574, 592, 600 mg of Re per kg of body weight lived without showing any visible symptoms; 3 rats receiving 830, 870, 890 mg of Re suffered from symptoms which vanished in a few hours or, at the latest, over night; 2 rats receiving 1050 and 1380 mg of Re died 60 and 30 minutes later respectively. The series places the lethal dose in the range 900-1000 mg of Re per kg of body weight. The small quantity of $NaReO_4$ available prevented the determination of this dose to a narrower range.

Immediately after an injection of the larger doses of rhenium the rats became pale and cyanotic. For at least an hour the respiratory rate and amplitude was increased, the respiration becoming laborious at times. A few minutes after the injection the tail and rear legs became rigid and extended, or they alternated between rigid extension and convulsions resembling somewhat those produced by strychnine. The convulsions could be induced by mild stimuli such as by tapping the cage, or by stamping on the floor. The front legs were never involved in the convulsions. The rats were able to right themselves but dragged their rear legs as they moved, propelled entirely by the front legs. The symptoms following a sublethal dose lasted for a few hours but disappeared completely and without showing any residual paralyses on the following morning.

[1] Hurd, L. C., Colehour, J. K., and Cohen, P. P. PROC. SOC. EXP. BIOL. AND MED., 1933, **30**, 926.

Molybdenum. Because rhenium is associated with molybdenum minerals on the earth's crust, similar toxicity studies were conducted with molybdenum salts. Intraperitoneal injections of a sodium molybdate solution (25 mg Mo per cc) into 20 rats weighing from 140-260 g produced a lethargy. The rats curled themselves into a sphere, retained normal posture but refrained from any movement. As the duration of the action increased, the depth of the lethargy increased until the rats expired quietly in this state. The 10 rats receiving 47, 69, 73, 86, 91, 92, 95, 104, 113, and 114 mg Mo per kg weight showed a few transitory symptoms and remained well; the 10 rats receiving 117, 121, 137, 155, 156, 175, 178, 185, 245, and 350 mg Mo per kg weight died quietly within a few hours or over night. The lethal dose is between 114 and 117 mg Mo per kg weight or approximately one-eighth that of Re.

Other Rhenium Compounds. Solutions of the salts K_2ReCl_6 and $ReCl_3$, injected intraperitoneally into mice were toxic. These salts acted probably through the HCl liberated in the hydrolysis $K_2ReCl_6 + 2\ H_2O \rightleftarrows ReO_2 + 4\ HCl + 2\ KCl$ and $2\ ReCl_3 + 3\ H_2O \rightleftarrows Re_2O_3 + 6\ HCl$. Equivalent injections of HCl or $FeCl_3$ killed the mice in the same manner. A black precipitate of insoluble ReO_2 or Re_2O_3 covered the peritoneum at autopsy.

Blood Studies. Hammett[2] reported that subcutaneous injections of germanium dioxide (6.6 and 45 mg per kg of body weight) produced a polycythemia of 1-5 million cells lasting 10-14 days after the injection. In recent years other students[3] have demonstrated the erythropoietic action of cobalt. For a study of the erythropoietic action of rhenium, 6 male albino rats weighing 188-243 g, normal to all appearances, were placed on a Steenbock ration with ample water and good housing. From October 3 to October 21, (the control period) semi-weekly determinations of the weight, hemoglobin, erythrocytes, and leucocytes were made. From October 21 until December 16 aqueous solutions of $NaReO_4$ (40-230 mg of Re per kg of body weight) were injected subcutaneously at intervals of 2 or 3 weeks. Since the largest injection was about one-fourth of the minimal lethal dose, the rats did not exhibit any of the symptoms which appear with the large doses. Weekly determinations (and in 2 rats daily determinations) of hemoglobin, erythrocytes, leucocytes, weight and the general well being of the rats after the injections show that Re does not have any erythropoietic action and that the slight progressive decrease in erythrocytes and hemoglobin is

[2] Hammett, F. S., Müller, J. H., and Nowrey, J. E., Jr., *J. Exp. Med.*, 1922, **35**, 173, 507.

[3] Orten, J. M., *Am. J. Physiol.*, 1936, **114**, 414.

TABLE I.

Date	Wt in g	Hemoglobin, g/100 cc blood	Erythrocytes in 10^6 per cu mm of blood
Oct. 3	210	13.4	10.5
" 14	243	13.8	7.5
" 19	259	16.9	8.1
" 21*	257	—	—
" 24	—	18.5	10.0
" 31	263	17.8	10.5
Nov. 9	271	14.8	8.4
" 13†	270	—	—
" 14	268	19.4	7.5
" 15	—	19.4	7.5
" 16	—	—	7.8
" 17	267	14.0	8.0
" 18	—	—	8.0
" 19	252	13.0	7.0
" 20	—	16.0	6.3
" 21	—	17.5	5.3
" 22	263	13.8	7.25
" 23	—	14.9	7.0
" 24	268	13.2	6.2
" 25	—	12.5	7.2
" 26	256	13.9	8.0
" 27	—	11.4	6.4
" 28	261	12.1	6.5

*Injected 10.9 mg Re per kg of rat intraperitoneally.
†Injected 58 mg Re per kg subcutaneously.

a secondary anemia due to frequent bleedings. A protocol for one rat receiving the largest amount of $NaReO_4$ appears in Table I.

Effects Upon Blood Pressure in Dogs. In a 5.5 kg dog under ether anesthesia and premedicated with morphine the mean femoral pressure rose from 108 to a maximum of 130 mm and returned to 108 mm after 5 minutes; the heart rate rose from 150 to 198 beats per minute after an intravenous injection of 25 cc of $NaReO_4$ solution containing 19 mg Re per cc. (86 mg per kg.)

An equal volume (25 cc) of normal saline solution injected intravenously both before and after the Re injection produced a temporary rise of 4 and 10 mm in blood pressure respectively.

In a 13.7 kg dog, the intravenous injection of 42 cc of $NaReO_4$ solution containing 20.4 mg Re per cc (62 mg per kg) increased the mean pressure from 118 to 144 mm for several minutes and decreased the heart rate from 102 to 96 beats per minute.

A 30 cc volume of normal saline solution injected intravenously into the preceding dog elevated the mean femoral pressure temporarily from 116 to 120 mm (4 mm), the heart rate changing from 96 to 102 beats per minute. The respiratory rate and amplitude were not disturbed by these injections of rhenium.

Discussion and Summary. Although about 20 of the rare elements have received some attention in pharmacology and some of these (thallium, gallium) have distinctive properties, rhenium surprises observers by its relatively low toxicity and general inertness in the body. The lethal dose for rats is of the order 900-1000 mg per kg of body weight. In rats it lacks the hemopoietic stimulus of Cobalt or Germanium, develops visible symptoms only in large doses, and produces only small transitory changes in blood pressure. Symptoms resembling the convulsions produced by strychnine suggest that the spinal cord has a high selectivity for the salts of Re.

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Partition Studies on the Clot-Aiding and Related Blood Phospholipids.

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The phospholipid *cephalin* is a potent coagulation (thromboplastic) agent[1] and a natural blood constituent. Elucidation of its distribution and physicochemical state is needed to define its rôle in clotting mechanisms.

The coagulation defect in hemophilia is inadequately remedied by cephalin *(in vitro)*. Trypsin (thromboplastic enzyme[2]), however, restores the normal coagulation properties, especially under optimal conditions with respect to the calcium and phospholipid factors.[3] The cephalin content of the blood platelets, including hemophilic, has been investigated previously.[4] With the aid of recently developed micromethods,[5] the following data (Table I) have been

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1 Ferguson, J. H., *Am. J. Physiol.*, 1938, **123**, 341.

2 Ferguson, J. H., and Erickson, B. N., *Am. J. Physiol.*, 1939, **126**, 661.

3 Ferguson, J. H., *Am. J. Physiol.*, 1939, **126**, 669.

4 Erickson, B. N., Williams, H. H., Avrin, I., and Lee, P., *J. Clin. Inv.*, 1939, **18**, 81.

5 Erickson, B. N., Avrin, I., Teague, D. M., and Williams, H. H., *J. Biol. Chem.*, 1940, **135**, 671.