coagulation which can be produced in a rabbit by the injection of 12 to 25 mg per kilo of trypsin can be prevented by the prior injection of a large dose of heparin (Table II). Likewise, blood which is incoagulable as the result of an injection of 5 mg per kilo of trypsin can be made to coagulate by the addition of further amounts of trypsin. This latter result demonstrates that the loss of coagulability is not due to a destructive action of trypsin upon any of the blood elements essential to its coagulation and indicates that the intravenous injection of shocking doses of trypsin leads to the liberation of sufficient heparin to more than counterbalance the direct coagulant effect of the injected trypsin.

Summary. The intravenous injection of trypsin in doses of 1 to 2 mg per kilo in dogs, or 3 to 7 mg per kilo in rabbits produces a varying degree of incoagulability of the blood. As the addition of similar concentrations of trypsin to blood *in vitro* does not produce this incoagulability, the latter appears to be an indirect effect. The addition of suitable amounts of protamine restores the coagulability to normal, indicating that the coagulation defect is due to heparin, presumably liberated *in vivo* from various tissues such as the liver.

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Effect of Radio-Phosphorus on Blood of Monkeys.*

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Radioactive phosphorus can be administered to animals and man in the form of sodium phosphate in doses sufficient to produce a decrease in the number of white blood cells.[1, 2] In order to obtain further data on the effect of radiophosphorus on the blood of normal animals with respect to the maximum dosage which can be tolerated,

* This investigation was supported by a grant from the John and Mary R. Markle Foundation.

† We wish to thank the various members of the staff of the Radiation Laboratory, whose generous coöperation makes radio-phosphorus available for biological and medical investigations.

1 Scott, K. G., and Cook, S. F., *Proc. Nat. Acad. Sci.*, 1937, **23**, 528.

2 Lawrence, John H., Scott, K. G., and Tuttle, L. W., *The New International Clinics*, 1939, 35-58.

4 young monkeys *(Macacus rhesus)* were given radiophosphorus as a solution of neutral isotonic sodium phosphate intraperitoneally in varying doses. Prior to the administration of radiophosphorus blood samples were collected so that the total red count, white count, and differential count could be determined. Blood samples were taken thereafter at intervals.

Results. An examination of Table I shows that all blood cells drop after administration of radiophosphorus in the dosages used. With respect to the time of maximum drop after radiophosphorus administration it appears that lymphocytes are affected first, the lowest levels appearing 14-21 days in monkey No. 1, 9-13 days in monkey No. 2, and 7-10 days in monkey No. 4. Since monkey No. 3 died from the radiation the lowest level of lymphocytes was observed from 35 to 43 days, a short time before death. The absolute number of granulocytes (polymorphonuclear leucocytes, eosinophiles, and monocytes) reached the lowest levels at a later date: 21-28 days for monkey No. 1, 23-37 days for monkey No. 2, 35-43 days for monkey No. 3, and 22-26 days for monkey No. 4. Red blood cells also were affected at later dates than lymphocytes and were more comparable to granulocytes in this respect.

In these experiments cells presumably originating from the bone marrow are depressed for a longer period of time than lymphocytes. This can be explained on the basis of the greater retention of P_{32} by bone marrow than by other tissues.[2, 4] The excretion of P_{32} by the monkeys used in this work was not measured. However, it can be assumed that radiophosphorus retention in monkeys is similar to that observed in mice and man.[2, 4, 5] After an original retention of 60 to 70% of the total dose, radiophosphorus is slowly excreted in urine and feces (5 to 7% per day loss due to excretion and decay).

A comparison of the percentage of blood cells remaining in monkey blood after P_{32} administration shows that granulocytes and lymphocytes are similarly affected. During the period of maximum effect the percentage of granulocytes in blood decreased to 3, 3, 5, and 2% of the absolute numbers present prior to P_{32} administration. With respect to lymphocytes the absolute number present dropped to 14,

[3] Lawrence, John H., *Nuclear Physics and Therapy.* Preliminary Report on a New Method for the Treatment of Leukemia and Polycythemia.

[4] Lawrence, John H., and Scott, K. G., PROC. SOC. EXP. BIOL. AND MED., 1939, **40**, 694.

[5] Lawrence, John H., Tuttle, L. W., Scott, K. G., and Connor, E. L., *J. Clin. Invest.*, 1940, **19**, 267.

TABLE I.
Effect of Radiophosphorus on the Blood of Monkeys (*Macacus rhesus*), counts per mm³.

Monkey	Radiophosphorus	Days after radiation	Red blood cells (millions)	White blood cells ×100	Granulocytes (absolute number) ×100	Lymphocytes (absolute number) ×100
No. 1	2 M. C. P_{32}	0	6.8	130	74	56
Male. 7 lbs.	1.3 M. C. P_{32}	7	6.6	60	47	13
Sacrificed 28th day.		14	4.6	12	4	8
Grossly tissues		21	4.7	13	2	11
appeared normal.	Sacrificed	28	3.8	24	3	21
No. 2	3.8 M. C. P_{32}	0	5.6	320	150	170
Male. 5 lbs.		9	6.5	37	19	18
		13	6.0	53	46	7
		23	4.8	15	5	10
		37	3.0	28	12	16
		43	4.0	60	28	32
		58	5.0	100	54	46
		102	4.5	156	32	124
		139	5.0	244	64	180
Alive and well. Wt 7.5 lbs.		436	5.5	131	43	88
No. 3	1.3 M. C. P_{32}	0	6.2	110	40	70
Male. 7.5 lbs.	7.15 M. C. P_{32}	30	5.1	44	18	26
Died 47 days		35	3.8	16	12	4
after P_{32} administration. Hemorrhagic areas under skin and in intestinal tract. Bone marrow appeared to be entirely hemorrhagic.*	Died	43	4.7	12	2	10
		47				
No. 4	4.97 M. C. P_{32}	0	4.8	200	70	130
Female. 7 lbs		7	5.2	43	37	6
at start, 10 lbs		10	5	26	24	2
at end		22	4.2	8	2	6
		26	3.8	6	1	5
		34	2.8	26	21	5
		44	3.0	46	26	20
		56	4.0	58	13	45
		120	4.2	114	38	76
Alive and well.		318	4.3	134	50	24

*Postmortem examination was carried out 7 hours after death. Microscopic studies revealed the following: *Liver,* no circulating white blood cells. Much edema. *GI tract,* lymphoid follicles absent, practically no cells in submucosa, some interpapillary edema. *Lymph nodes,* absence of normal architecture, follicles frequently devoid of all cells except the stromal cells. *Kidney,* a rare area of cellular degeneration. *Lung,* no significant changes except for some edema. *Spleen,* marked hypocellularity, but normal architecture. *Marrow,* almost complete aplasia, some adult red cell congestion in areas; in general the most important findings were the complete absence of white blood cells in the tissues and the severe aplasia of the marrow and the hypoplasia of the spleen and lymph nodes.

4, 6, and 2% of those present prior to P_{32} dosage (monkeys 1-4 inclusive). Red cells do not appear to be as radio-sensitive. During the maximum effect the red cell count dropped to 47%. Al-

though eosinophiles and monocytes are included in the total granulocyte count, they were identified separately and are affected in the same manner as the polymorphonuclear leukocytes.

Regarding dosage it was found that 1.04 millicuries of radiophosphorus per pound of body weight was fatal (monkey No. 3). However, dosages of .76 and .71 millicuries of radiophosphorus per pound of body weight were tolerated by monkeys No. 2 and No. 4. These monkeys are still alive and appear to be in good health. This level of radiophosphorus dosage would be roughly equivalent to 114 millicuries in one dose to a 150-pound man, this being 10 or more times the dosage used therapeutically in this laboratory. The lethal dosage in small mammals also appears to be comparable. Mice will tolerate as much as 1.36 millicuries of radiophosphorus per pound (unpublished work).

Conclusions. 1. Radiophosphorus lowers the absolute numbers of red cells, lymphocytes, and granulocytes in monkeys. 2. The degree of effect is about the same in lymphocytes and granulocytes, red cells being less affected. 3. Monkeys tolerated dosages of .76 and .71 millicuries of radiophosphorus per pound of body weight, 1.04 millicuries per pound being fatal. 4. The tolerance levels of radiophosphorus are about 10 times that usually used therapeutically.

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Regulation of Skin Temperatures after Lesions of Spinal Nerve Roots.

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The observation has been made that after deafferentation of a hindlimb, the skin temperatures recorded from the footpads of that limb are lower than those in the opposite normally innervated extremity.[1, 2, 3] However, it was found that when such animals were subjected to bilateral abdominal sympathectomy, there was no significant difference in the skin temperatures recorded from the

1 Hinsey, J. C., and Cutting, C. C., *Anat. Rec.*, 1932, **52**, 57.

2 Hinsey, J. C., *Am. J. Physiol.*, 1934, **109**, 53.

3 Zuckerman, S., and Rueh, T. C., *Am. J. Physiol.*, 1934, **109**, 116.