CATION EXCHANGE BETWEEN CELLS AND PLASMA OF MAMMALIAN BLOOD

II. Sodium and Potassium Exchange in the Sheep, Dog, Cow, and Man and the Effect of Varying the Plasma Potassium Concentration

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Early experiments on the measurement of sodium exchange between the cells and plasma of mammalian blood, have been reported by Cohn and Cohn (1), Eisenman *et al.* (2), and Hahn and Hevesy (3). Studies of potassium exchange in the blood of species other than man are described by Hahn *et al.* (4) and by the University of Rochester group in addition to their studies on human blood (5–7). Many of these previous experiments were intentionally only semiquantitative. Attempts to obtain more precise determinations of exchange rates were often complicated by difficulties in obtaining sufficiently large specific activities, in establishing suitable radiochemical purity of the radioactive material, and in maintaining consistently reliable behavior of the instruments for activity measurement. The experiments *in vitro* usually lacked acceptable evidence that the system was in a properly viable state. The experiments *in vivo* were complicated by lack of the necessary number of measurements to permit quantitative studies in a more physiological system. Nevertheless it was possible to establish that the cellular elements of blood from many different species were able to exchange their sodium or potassium ions with those in the surrounding plasma. Rough estimates of the kinetics of the exchange processes were also usually obtained.

Recent success in eliminating many of these difficulties has led to an investigation of the exchange of potassium *in vitro* between the cells and plasma of human blood (8). Preliminary observations of potassium exchange in canine blood were discussed in an earlier report (9). This communication presents results and a summary of studies of the exchange of potassium and sodium in the blood of the dog, cow, sheep, and man. In contrast to the straightforward situation in human blood, potassium exchange in the dog is complicated by the existence of two fractions which exchange at widely different rates. One fraction containing the buffy coat cells exchanges rapidly, whereas the fraction containing the erythrocytes exchanges slowly. Such an explanation fails to account for the inhomogeneity in the results for sodium exchange in human blood.

Although not established as a universal rule, preliminary results reported here indicate a rough correlation in different species between the exchange rate for potassium and the intracellular concentration of this ion. In human blood, the potassium exchange rate is remarkably independent of the concentration of the plasma potassium. These results again strongly suggest that the earlier concept of cation impermeability must be replaced by a biological regulation process.

EXPERIMENTAL

Donors.—Canine blood was obtained by jugular puncture from four different dogs, two males, and two spayed females. The animals were maintained in good health on Gaines dog meal. Supplementary iron was rarely required since the hematocrit readings were usually greater than 50 per cent. The blood was ordinarily drawn about 20 hours after feeding.

Bovine blood was obtained either from a pregnant 3 year old cow or a yearling bull calf. Both animals were apparently in good health. They were members of the Hereford herd originally brought to Oak Ridge for observation after the Alamogordo test explosion, and were born after this event.

Sheep blood was obtained from a 5 month old Hampshire Down female lamb. This animal when purchased was suffering from intestinal parasites. Further observation disclosed a blood parasitic infestation of uncertain etiology. Experimental work was postponed for a period of therapy lasting about 6 weeks. During this time the hematocrit reading rose from 10 to 30 per cent and an apparently normal blood picture was obtained.

Methods.—The blood was maintained *in vitro* by the procedure described in the previous paper. Preliminary experiments with dog blood using an alternative method are described elsewhere (9). In sodium studies, smaller amounts of carbonate were activated since the molal specific activities of sodium obtained from slow neutron irradiation are about twenty times greater than for potassium. As before, in the experiments designated by A, samples of cells and whole blood were analyzed and the results for the cells were obtained by difference. In the B experiments, both cells and plasma were analyzed directly. After centrifugation, in the sodium experiments, the top layer of cells was washed with isotonic KCl instead of NaCl. All experiments were conducted at 38°C.

In experiments in which the fraction containing the white cells was to be removed from canine blood, the cells were centrifuged loosely and the top layer removed. This was repeated three times. Smears were then examined to check the completeness of the separation. The operation usually produced perceptible hemolysis.

Addition of Sugar.—Danowski (10) has demonstrated that potassium leakage from human cells at 38°C. coincides with the depletion of the blood sugar and that this effect may be prevented for longer periods by the addition of sugar to the plasma. The effect in canine blood has been investigated in these experiments. Fig. 1 shows the increase in plasma potassium which occurs as the blood sugar becomes exhausted. *In vitro*, the blood of the dog is much less stable against osmotic disturbance than that of the human being. However, its deterioration is definitely retarded when sugar is

added. As in the experiments on human blood dextrose was added in all cases, increasing the whole blood concentration to about 350 to 400 mg. per cent. The criteria of stability were the same as in the human experiments. In all cases except human blood, the plasmas were sufficiently light colored that the threshold of visible hemolysis corresponded to the lysis of about 0.1 per cent of the cells.

Alteration of Plasma Potassium.—Dowex-50 ion exchange resin was converted to the potassium form by neutralizing the hydrogen resin with KOH. This was then washed and shaken with fresh plasma. By using the proper ratio of resin to plasma an arbitrarily controlled amount of sodium may be replaced with potassium with

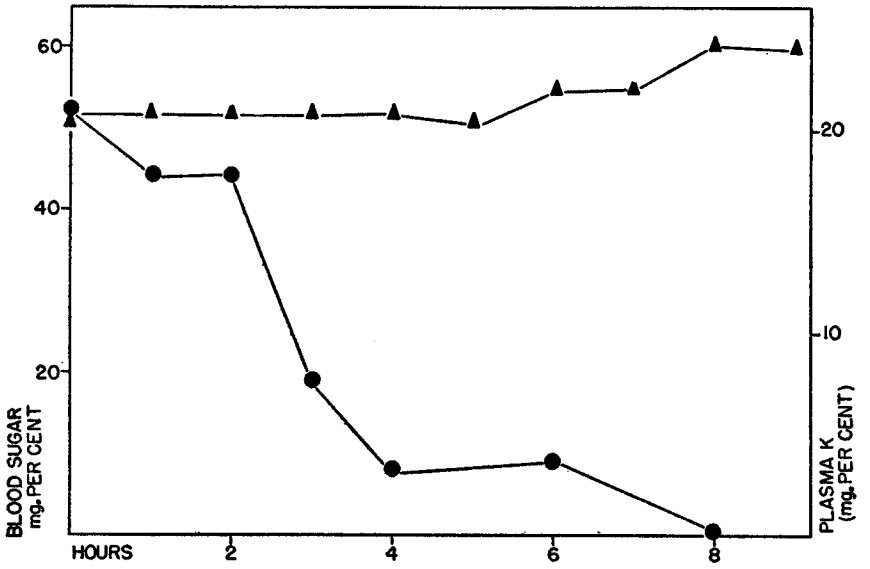

FIG. 1. Changes in canine blood *in vitro*. The left hand scale and solid circles represent the blood sugar. The right hand scale and solid triangles, the plasma potassium concentration.

minimal alteration in the osmotic pressure. Although the procedure removes calcium, the effect is small since only a small fraction of the treated plasma appears in the final suspension medium. After potassium determinations on the treated plasma, it was mixed in adjustable proportions with the untreated to form the tagging solution, which was then used in the same way as before.

RESULTS

Potassium Exchange in Canine Erythrocytes.—It was previously shown (9) that mature canine erythrocytes exchange potassium slowly and that the initial rapid decline in plasma specific activity is due to the presence of a rapidly exchanging fraction associated with the white cells. Further studies of canine blood, including determinations of indices of cell stability, show that deteriora-

tion occurs considerably more rapidly than in the human case. Often the observations obtained beyond the first 2 or 3 hours could be accepted only with reservations. Since the initial points are to be favored, it is preferable to remove the rapidly exchanging fraction if the true erythrocyte exchange rate is to be properly determined. Table I shows the results of the best experiment (Experiment 10 A). The elevation of the first point is caused by an abnormally low potassium concentration. This effect was observed in three other instances

TABLE I

Potassium Exchange in Canine Blood from Which the White Cell Fraction Has Been Removed
Experiment 10 A

Blood drawn.....1:30 p.m.
Experiment started.....5:42 p.m.
Canine donor
Arterial saturation....O_2, 14 per cent, CO_2, 6 per cent, N_2, 80 per cent
Commercial heparin
Initial hematocrit reading.....50 per cent

Sample No.	Time	Hemolysis	Hematocrit reading	Counts/min./cc.		Potassium concentration, *mg. per cent*		Relative specific activity	
				Plasma	Whole blood	Plasma	Whole blood	Plasma	Cells
	min.		*per cent*						
1	2	+++*	40.7	1102	1282	13.7	16.8	1.11‡	0
2	20	+++	42.7	1130	1307	15.2	16.0	1.0	0.012
3	36	+++	42.6	1090	1271	15.2	15.5	0.99	0.013
4	68	+++	41.5	1081	1276	15.2	16.0	0.99	0
5	96	+++	42.4	1089	1318	15.2	16.0	0.96	0.061
6	122	+++	—	1100	1281	15.2	15.9	0.99	—
7	184	+++	42.0	1075	1312	15.8	16.0	0.90	0.065
8	240	+++	—	1155	1350	15.8	15.9	0.95	—
9	300	+++	42.5	1080	1340	15.6	15.9	0.90	0.089
10	875	+++	44.0	945	1267	16.0	16.0	0.81	0.14

* Corresponds to the lysis of about 1 per cent of the cells.
‡ Results relative to sample 2 instead of 1.

in the canine experiments and merits further investigation. In Experiment 10 A the blood was equilibrated under gas containing 14 per cent oxygen to simulate the arterial condition. When the hemoglobin was reduced using 6 per cent oxygen similar results were obtained (Experiment 11 B). However, the determination of the exchange rate is less satisfactory since a slow potassium leakage occurred from the cells to the plasma. Of three other experiments one showed the presence of a reduced but incompletely removed white cell fraction and two others were unsatisfactory because of irregularities in the hematocrit readings and in the radioactivity curves. The specific activity variations for Experiment 10A are shown in Fig. 2.

Specific Activity Changes in Canine Whole Blood: Interpretation.—The changes which occur in whole blood are best shown in Experiment 4 A (Table II). Fig. 3 shows the specific activity variations. Two other experiments were in satisfactory agreement although a greater fluctuation of the points from a smooth curve occurred, and other difficulties of the sort already indicated were present. The results show clearly that an initially rapid phase is superimposed on a slow linear decline. The slow portion is readily identified as the initial part of an exponential of very large half-value time. The curve is analyzed by drawing a tangent to the last few points and extrapolating to zero time. The differ-

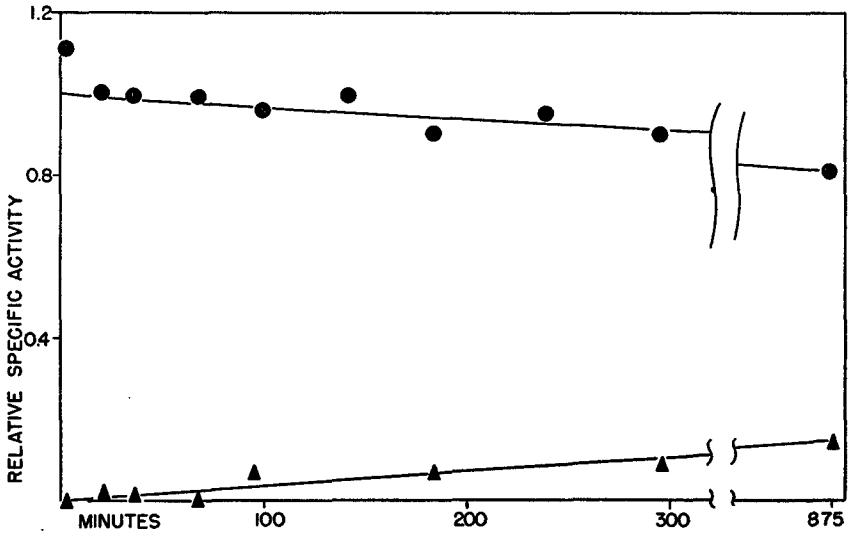

FIG. 2. Potassium specific activity changes in plasma (solid circles) and cells (solid triangles) of canine blood from which the white cell fraction was removed (Table I).

ences between the ordinate values of the curve and the tangent are then plotted on semilogarithmic coordinates (Fig. 4). The resulting data fit fairly closely to a straight line which demonstrates that the rapid phase is also exponential in character although there may be some inhomogeneity of exchange rates as emphasized previously in the interpretation of experiments on human erythrocytes.

The theoretical behavior of a system containing a fast and a slow fraction is discussed in detail in a separate communication (11). When a large difference exists between the exchange rates it is possible to make a convenient approximation. The fast fraction exchanges as though there were no exchange between the cells of the slow fraction and the plasma. Following this a slow exchange occurs between the slow fraction and the combination of the plasma and fast fraction.

TABLE II

Potassium Exchange in Canine Whole Blood

Experiment 4 A

Blood drawn.....2:35 p.m.
Experiment started.....3:57 p.m.
Canine donor
Venous saturation....O_2, 5 per cent, CO_2, 8 per cent, N_2, 87 per cent
Commercial heparin
Initial hematocrit reading.....49.0 per cent

Sample No.	Time	Hemolysis	Hematocrit reading	Counts/min./cc.		Potassium concentration, *mg. per cent*		Relative specific activity	
				Plasma	Whole blood	Plasma	Whole blood	Plasma	Cells
	min.		*per cent*						
1	2	—	40.3	690	455	15.8	23.9	1.00	0.01
2	17	—	40.3	672	457	16.0	24.0	0.95	0.03
3	35	+	40.3	632	447	16.0	24.0	0.93	0.05
4	49	+	39.9	621	448	16.0	23.6	0.89	0.07
5	66	+	40.5	615	448	16.3	24.6	0.87	0.07
6	90	+	39.9	609	461	16.9	23.9	0.81	0.10
7	124	+	41.1	580	447	17.6	25.4	0.76	0.11
8	188	+	41.0	543	447	17.2	25.4	0.73	0.14
9	304	+	41.0	553	444	19.8	24.0	0.65	0.16
10	420	+	40.7	581	400	19.0	24.6	0.80	0.05
11	540	+	41.6	540	475	18.4	24.8	0.64	0.19

The equation describing the specific activity changes in the plasma under this approximation is

$$a_1/a_0 = A + Be^{-k_1 t} + Ce^{-k_2 t}$$

where a_1 is the plasma specific activity at time t, a_0 the initial value of a_1,

$$A = S_1/S,\ B = S_1S_3/S\ (S_1 + S_2),\ C = S_2/(S_1 + S_2),$$

S is the total potassium, S_1 the plasma potassium, S_2 the potassium in the fast fraction, and S_3 that in the slow fraction. The exponential constants are

$$k_1 = \rho_3 S/[S_3(S_1 + S_2)],\ k_2 = \rho_2(S_1 + S_2)/S_1S_2$$

where the ρ's are the corresponding exchange rates.

By applying the equation to the results of Experiment 4 A, an estimate of the amount of rapidly exchanging potassium and of its percentage rate of exchange can be obtained. The results are given in Table III, which also includes the results of Experiments 10 A and 11 B in which only the slow exchange is obtained. From the intercept of the tangent in Fig. 3, it appears that in Experiment 4 A the ratio $S_2/(S_1 + S_2)$ is about 0.32, and thus the rapidly ex-

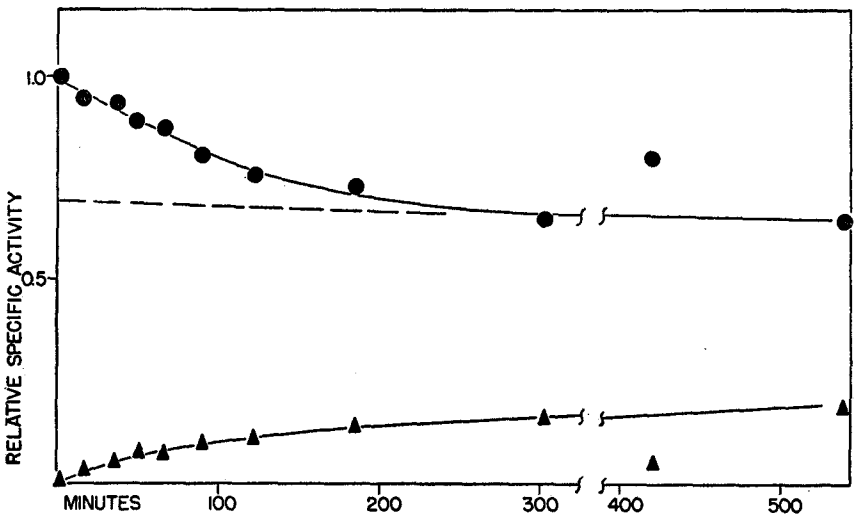

FIG. 3. Potassium specific activity changes in plasma (solid circles) and cells (solid triangles) of canine whole blood. The dotted line is the tangent to the right hand portion of the plasma curve. By subtracting points on this line from corresponding points on the plasma curve the contribution of the rapidly exchanging fraction (Fig. 4) is obtained.

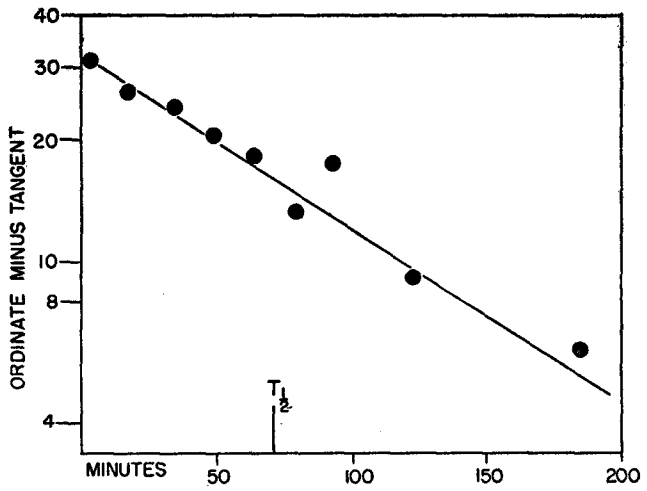

FIG. 4. Semilogarithmic plot of the rapidly exchanging fraction (Fig. 3). The half-value time $T_{1/2}$ is 70 minutes.

changing fraction represents about 20 per cent of the total blood potassium. From the difference in the whole blood potassium concentrations in Experiments 4 A and 10 A, it would appear that about 35 per cent of the total potas-

sium of the blood is removed with the fraction containing the white cells. This result is less reliable and is in error in part, due to the lack of comparability of the bloods in the two experiments. If we assume that the fast fraction is in the white cells whose relative volume might be 1 per cent then the ratio of concentration of potassium between these cells and the rest of the blood must be at least 20 to 1.

Wilson and Manery (12) report a fairly high concentration of potassium in rabbit white cells. These cells have a relatively high exchange rate for sodium and potassium (13). In an attempt to determine the potassium content of canine white cells, suspensions of the buffy coat were made in plasma. From analyses of the suspension and of the plasma and from white cell counts, it was inferred that, in canine blood, with an assumed normal count of 15,000 cells per c.mm., about 15 per cent of the whole blood potassium is in the white

TABLE III

Potassium Exchange Rates in Canine Blood

Experiment No.	Gas saturation	Rapidly exchanging fraction	Transport rates*		
			Erythrocytes to plasma	Plasma to erythrocytes	Rapid fraction
			per cent/hr.	*per cent/hr.*	*per cent/hr.*
4 A	Venous	Present	~0.5‡	~0.5‡	~30
10 A	Arterial	Removed	1.4	1.4	—
11 B	Venous	Removed	2.8	1.4	—

* Per cent of potassium in cells which are exchanging.

‡ Uncertain because of presence of rapidly exchanging fractions.

cells. This is a lower limit since definite evidence was obtained of potassium leakage from the cells. In one series of experiments preliminary attempts were made to separate viable white cells from dog blood by flotation with bovine albumin or by differential sedimentation. The results of studies of potassium exchange in the white cell concentrates were equivocal and further investigation is required. Although the results favor the effect of white cell potassium on the inhomogeneity of exchange in dog blood nevertheless the existence of more than one white cell series and the inhomogeneity of the interior of the white cell are all points which await further clarification. It should also be noted that the fraction removed with the white cells also includes some of the young erythrocytes.

Potassium Exchange in Bovine and Sheep Blood.—Single studies were made of potassium exchange in bovine and sheep blood. The results which are given in Tables IV and V include the usual records of hematocrit readings and plasma potassium values. Although there was detectable hemolysis in the bovine experiment there is otherwise little evidence in either case of instability during the relatively short periods of observation.

In contrast to the canine experiments the specific activity curve for cow blood (Fig. 5) shows no detectable evidence of an initial rapid exchange. We

TABLE IV

Potassium Exchange in Bovine Blood
Experiment 20 B

Blood drawn.....9:30 a.m. Venous saturation....O_2, 6 per cent, CO_2, 6 per cent, N_2, 88 per cent
Experiment started.....11:20 a.m.
Bovine donor Sodium heparin salt
Initial hematocrit reading.....34.3 per cent

Sample No.	Time	Hemolysis	Hematocrit reading	Counts/min.		Potassium, *mg.*		Relative specific activity	
				Plasma	Cells	Plasma	Cells	Plasma	Cells
	min.		*per cent*						
1	2	+	30.5	1648	73	0.36	1.06	1.0	0.0
2	35	+	29.7	1653	125	0.36	1.05	0.977	0.009
3	90	+	29.9	1582	151	0.36	1.05	0.958	0.015
4	150	+++	30.1	1682	204	0.36	1.05	0.937	0.022
5	180	+	29.6	1621	210	0.36	1.04	0.930	0.025
6	240	+	29.8	1511	248	0.36	1.04	0.903	0.034
7	300	+	30.2	1505	300	0.36	1.04	0.877	0.041

TABLE V

Potassium Exchange in Sheep Blood
Experiment 21 B

Blood drawn.....10:00 a.m. Venous saturation....O_2, 6 per cent, CO_2, 6 per cent, N_2, 88 per cent
Experiment started.....11:05 a.m.
Donor.....female lamb Sodium heparin salt
Initial hematocrit reading.....34.9 per cent

Sample No.	Time	Hemolysis	Hematocrit reading	Counts/min.		Potassium, *mg.*		Relative specific activity	
				Plasma	Cells	Plasma	Cells	Plasma	Cells
	min.		*per cent*						
1	0	–	28.7	1781	49	0.44	0.38	1.0	0
2	30	–	29.2	1865	99	0.44	0.38	0.97	0.022
3	65	–	29.5	1840	116	0.45	0.40	0.94	0.038
4	120	–	29.8	1765	157	0.45	0.40	0.92	0.064
5	180	–	29.2	1815	—	0.45	—	0.97	—
6	240	–	29.7	1701	180	0.45	0.40	0.90	0.080

have previously pointed out (8) that the exchange rate in per cent of cell potassium per hour is the same as the initial hourly rate of increase of relative cell specific activity, which in this case is about 3.8 per cent per hour.

The initial slope method determines a unique exchange rate only where there is no evidence of multiplicity. This presents a difficulty in the case of

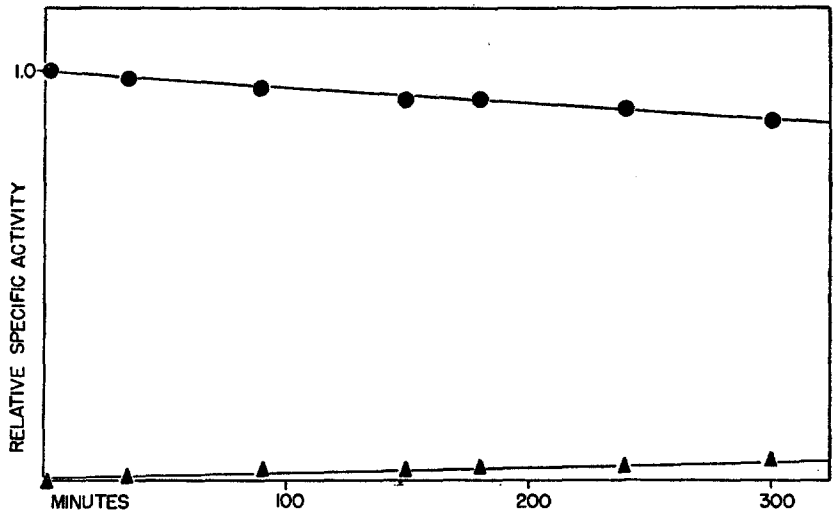

FIG. 5. Potassium specific activity changes in bovine blood.

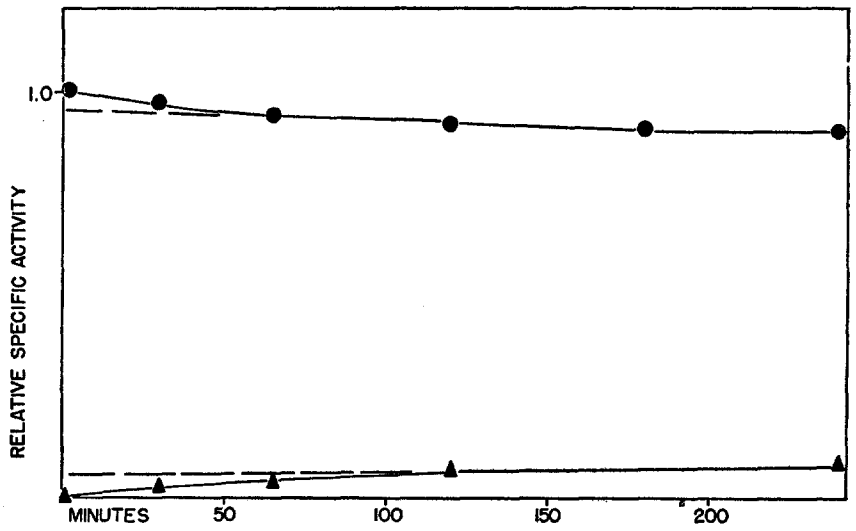

FIG. 6. Potassium specific activity changes in sheep blood. Note the slight initial curvature suggesting a small rapidly exchanging fraction.

sheep blood (Fig. 6) which shows a small but distinct rapidly exchanging fraction which represents about 2.5 per cent of the plasma potassium. The initial slope of the curve now determines a mean exchange rate for all the cells, namely

about 5 per cent per hour. If this be accepted as an upper limit the corresponding lower limit of about 0.5 per cent per hour is obtained as in the canine case

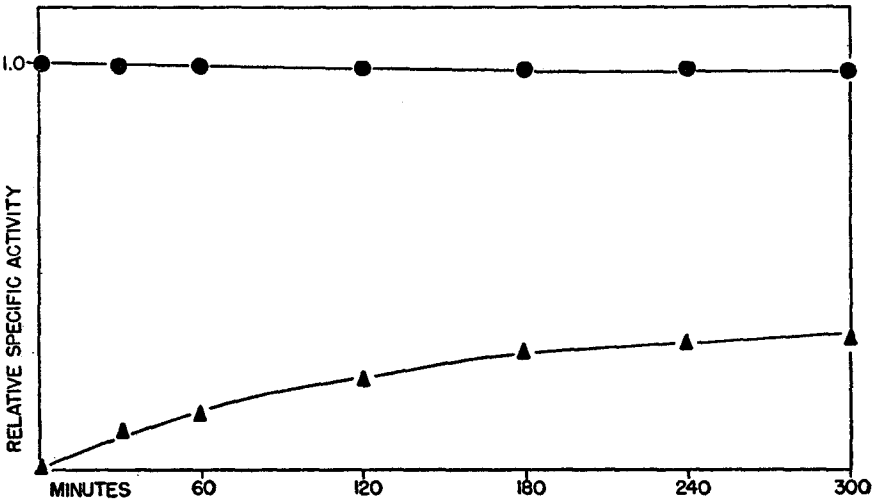

FIG. 7. Sodium specific activity changes in human blood.

TABLE VI

Sodium Exchange in Human Blood
Experiment 5 C

Blood drawn.....9:15 a.m.
Experiment started.....10:30 a.m.
Donor..human female type O Rh +
Venous saturation....O_2, 6 per cent, CO_2, 6 per cent, N_2, 88 per cent
Sodium heparin salt
Initial hematocrit reading.....38.3 per cent

Sample No.	Time	Hemolysis	Hematocrit reading	Counts/min.		Sodium, *mg.*		Relative specific activity	
				Plasma	Cells	Plasma	Cells	Plasma	Cells
	min.		*per cent*						
1	2	—	36.8	5770	125	6.40	0.28	1.0	0
2	30	—	36.4	5770	151	6.37	0.32	0.995	0.097
3	60	—	35.4	5970	170	6.38	0.31	0.995	0.13
4	120	—	35.0	5600	180	6.52	0.28	0.990	0.21
5	180	—	34.6	5870	206	6.42	0.28	0.987	0.29
6	240	—	34.5	5650	199	6.40	0.32	0.987	0.30
7	300	—	34.9	5250	204	6.40	0.32	0.980	0.32

from the slope of a tangent extended backward from the termination of the curve (Fig. 6).

Sodium Exchange in Human Blood.—The results of a typical investigation

TABLE VII

Sodium Exchange in Bovine Blood
Experiment 6 C

Blood drawn.....9:30 a.m. Venous saturation....O_2, 6 per cent, CO_2, 6 per
Experiment started.....10:30 a.m. cent, N_2, 88 per cent
Donor.....cow Sodium heparin salt
Initial hematocrit
reading.....30.9 per cent

Sample No.	Time	Hemolysis	Hematocrit reading	Counts/min.		Sodium, *mg.*		Relative specific activity	
				Plasma	Cells	Plasma	Cells	Plasma	Cells
	min.		*per cent*						
1	2	–	26.6	10,040	253	7.06	1.25	1.0	0
2	30	–	25.5	11,180	504	7.82*	1.34*	0.99	0.1
3	60	–	26.1	9,600	598	7.82*	1.34*	0.97	0.18
4	120	–	26.5	11,020	864	7.82	1.34	0.96	0.25
5	180	+	26.5	9,780	1053	7.82*	1.34*	0.93	0.38
6	240	–	26.2	10,440	1270	7.82	1.34	0.92	0.42

* Values assumed from samples 4 and 6, since actual determinations were ruined.

TABLE VIII

Sodium Exchange in Canine Blood
Experiment 7 C

Blood drawn.....10:00 a.m. Venous saturation....O_2, 6 per cent, CO_2, 6 per
Experiment started.....10:30 a.m. cent, N_2, 88 per cent
Donor.....dog Sodium heparin salt
Initial hematocrit
reading.....52.3 per cent

Sample No.	Time	Hemolysis	Hematocrit reading	Counts/min.		Sodium, *mg.*		Relative specific activity	
				Plasma	Cells	Plasma	Cells	Plasma	Cells
	min.		*per cent*						
1	2	+	45.1	6340	176	6.38	3.87	1.00	0
2	30	–	46.0	6240	470	6.44	3.99	0.96	0.074
3	60	–	45.5	5780	678	6.38	3.90	0.93	0.13
4	120	–	45.2	5300	1000	6.25	4.02	0.91	0.21
5	180	–	47.0	4810	1340	6.25	3.90	0.84	0.33
6	240	–	45.2	5140	1315	6.25	3.51	0.86	0.34
7	300	–	44.6	4525	1539	6.38	3.99	0.78	0.38

of sodium exchange in human blood at 38°C. are shown in Table VI and Fig. 7. The cellular specific activity curve rises at first more rapidly and later more slowly than a single exponential indicating non-uniformity in the cellular compartment. The system behaves as though about 45 per cent of the cellular

sodium were more readily exchangeable than the rest. However a correct interpretation of the result must await a more complete understanding of the nature of the cellular inhomogeneity. Lacking this we proceed as in the previous case and determine the upper and lower limits of 14 and 1 per cent per hour for the sodium in human cells. The lower limit was obtained by averaging the results of several other experiments of longer duration since the data in Fig. 7 do not extend beyond 5 hours.

In a search for the cause of the multiplicity effect it was found that the situation retains its characteristic features after removal of the buffy coat.

TABLE IX

Sodium Exchange in Sheep Blood
Experiment 9 C

Blood drawn.....9:00 a.m.
Experiment started.....11:16 a.m.
Donor.....sheep
Venous saturation....O_2, 8 per cent, CO_2, 8 per cent, N_2, 84 per cent
Sodium heparin salt
Initial hematocrit reading.....32.0 per cent

Sample No.	Time	Hemolysis	Hematocrit reading	Counts/min.		Sodium, *mg.*		Relative specific activity*	
				Plasma	Cells	Plasma	Cells	Plasma	Cells
	min.		*per cent*						
1	2	+++	26.3	1220	20	8.00	—	1.0	0
2	26	—	26.3	1192	30	8.45	2.09	0.99	0.036
3	87	—	26.7	1325	48	8.45	2.09	0.99	0.080
4	151	—	27.5	1305	54	8.45	1.88	0.98	0.10
5	183	—	27.5	1275	57	8.45	2.04	0.97	0.11
6	287	—	26.6	1400	81	8.45	2.00	0.97	0.17

* Values taken on basis initial plasma sodium 8.45.

Since the effect is found to be unaltered in cells which have been equilibrated for 4 hours before addition of the isotope it is not caused by a progressive variation in the exchange rate during the maintenance of the blood *in vitro*. Increasing the rocking rate of the flasks from 10 to 25 oscillations per minute failed to alter the result which might otherwise be attributed to incomplete mixing of cells and plasma. The possibility of contamination by K^{42} is remote since the activation of Na^{24} is greatly favored in isotope production. The data thus strongly suggest that the inhomogeneity in this case is within the erythrocytes themselves.

Sodium Exchange in Canine, Bovine, and Sheep Blood and Summary of Exchange Rates.—The results of short term experiments on sodium exchange at 38°C. in the other three species are given in Tables VII to IX. The specific activity curves (Figs. 8 to 10) do not show any detectable evidence of cellular

inhomogeneity. However it may be argued particularly in the case of sheep blood (Fig. 10) that the duration of the observations was insufficient to un-

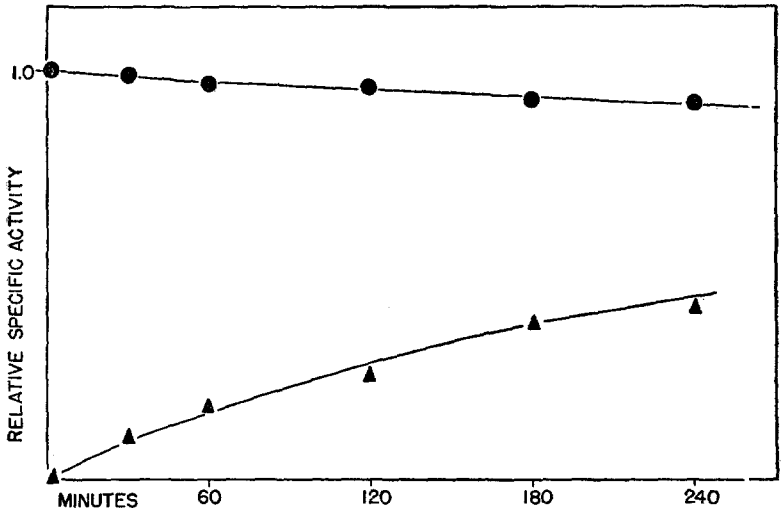

FIG. 8. Sodium specific activity changes in bovine blood.

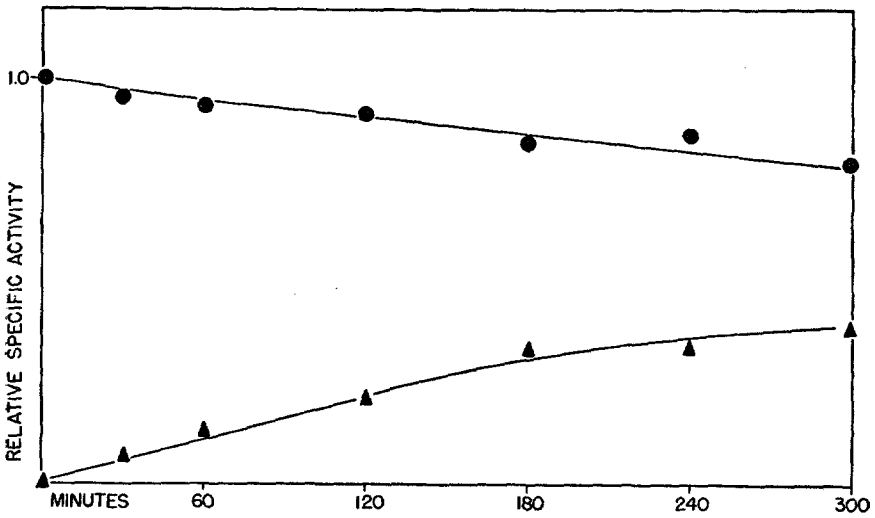

FIG. 9. Sodium specific activity changes in canine blood.

cover small effects. Since in these experiments the exchange rates are determined by the initial slope method the result obtained will be the mean of the individual exchange rates of the cellular population if inhomogeneity exists.

The sodium and potassium exchange rates or their limiting values for the

four species are summarized in Table X which also includes a few selected values from the earlier literature. The potassium exchange rates show a definite

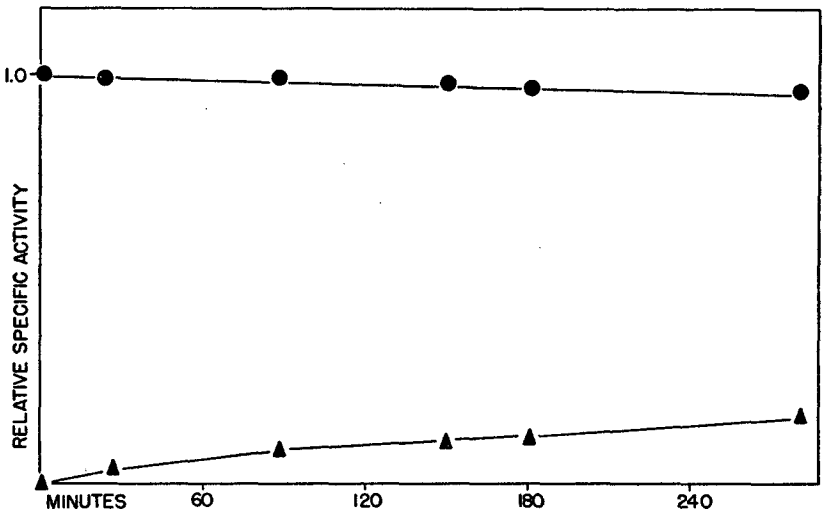

FIG. 10. Sodium specific activity changes in sheep blood.

TABLE X

Summary of Exchange Rates for Sodium and Potassium in Erythrocytes of Four Species Selected Results for Three Other Species Are Included from the Earlier Literature

Species	Cellular concentration		K exchange rate		Na exchange rate	
	K	Na				
	mM/liter	*mM/liter*	*mM/liter/hr.*	*per cent cellular K/hr.*	*mM/liter/hr.*	*per cent cellular Na/hr.*
Man	91	10.8	1.65	1.8	1.5–0.1	14–1
Cow	25	70	0.95	3.8	11	16
Sheep	11.5	82	0.5–0.05	5.0–0.5	4	5
Dog	5.5	106	0.055	1.0	13	12.7, (~17*)
Cat	6‡	104‡			~12§	10–15§
Rabbit	99‡	16‡	3.0	3.0¶		
Rat	100‡	12‡	~6	~6¶		

* Cohn and Cohn (1).
‡ Kerr (20).
§ Mullins *et al.* (5).
¶ Dean *et al.* (6).

correlation with the intracellular potassium concentration. The correlation of sodium exchange rate with intracellular cation is suggestive but less clear.

Effect of Alteration of Plasma Potassium Concentration.—In one experiment

three lots of human blood were mixed with ½ cc. quantities of tagging plasma in which varying amounts of potassium had been substituted for sodium. The specific activity data are shown in Table XI. It is seen that the resulting variations in half-value time almost completely compensate the variations in plasma potassium so that the absolute rate of exchange and hence the rate in per cent of cellular potassium per hour is, if anything, slightly depressed by the increase in plasma potassium. The depression may not actually be real since the over-all uncertainty is probably about 8 per cent.

TABLE XI

Effect of Alteration in Plasma Potassium Concentration

Plasma potassium		Relative specific activity			Half-value time	S_2/S_1	Per cent cell K exchanged per hr.
Total	Concentration	Time	Plasma	Cells			
mg.	*mg. per cent*	*min.*			*hrs.*		
0.42	19.5	0	1.0	0.0	1.8	12.4	2.9
		35	0.83	0.015			
		95	0.55	0.035			
		165	0.41	0.047			
0.66	31.0	0	1.0	0.00	2.9	7.9	2.7
		60	0.78	0.024			
		140	0.64	0.044			
		185	0.54	0.056			
1.21	57.0	0	1.0	0.0	4.8	4.3	2.7
		75	0.84	0.033			
		150	0.755	0.056			
		225	0.67	0.072			

DISCUSSION

The historical background of the earlier controversy as to whether or not erythrocytes are permeable to cations has been adequately summarized elsewhere (14). On the one hand the classical theory of electrolyte distribution in mammalian blood (15, 16) of necessity postulates cation impermeability (17). In contrast the pioneer isotope experiments seemed to show definite cation penetration. Since the resolution of the dilemma leads to the concept of active self-regulation by the cell of its cation requirements (18) the demonstration of cation penetration is of more than passing interest. Our previously reported results for potassium exchange in human blood (8) and those of Raker *et al.* (19) do more than merely confirm the earlier observations. They also establish such consistencies as the close agreement of exchange rates obtained in experiments independently conceived and executed in different laboratories, the

uniformity of the observed variation with temperature, and the independence of the exchange rate in plasma of variable potassium concentration. Included also are the smooth variations in plasma and cell specific activities and the close conformity of the results to theoretical predictions for a two compartment system. Considering this and other evidence the reality of potassium penetration of human red cells must be accepted.

When the observations are extended to include a survey of sodium exchange in man and sodium and potassium exchange in other species the results confirm the penetration of both cations. However, in some cases complications are encountered which are usually characteristic of kinetic experiments with isotopes in all but the most ideal situations. It was emphasized previously (8) that determinations of rates of transport of a substance between compartments require that the compartmental contents be uniformly mixed. When specific activity curves are obtained which do not follow a single exponential relation this criterion must fail in at least one compartment. One cause of cellular non-uniformity is the exchange of potassium in the buffy coat of canine blood, but such an explanation fails to account for the inhomogeneity of the sodium exchange in human blood. Thus individual cases must be considered separately and each solution will require considerable investment in time and effort.

These difficulties prevent the clear establishment of an unequivocal correlation in different species between the exchange rate for a given cation and its intracellular content. Nevertheless in the case of potassium the exchange rates in per cent of the cellular element per hour are roughly comparable whereas the absolute rates are highly variable. In the case of sodium the situation is less obvious although the percentage sodium exchange rates tend to be considerably higher than those for potassium. A correlation of exchange rate with intracellular concentration and a lack of dependence on extracellular concentration such as we observe for potassium are characteristic of a process of active maintenance of a stable internal milieu in a variable external environment.

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SUMMARY

Sodium and potassium exchange has been studied in the blood of the sheep, dog, cow, and man. The potassium exchange rate in human cells is practically unaltered by increasing the plasma potassium concentration approximately threefold. Comparing the results in different species the exchange rate for potassium shows a rough correlation with the intracellular amount of the element. Expressed in per cent of the cellular content sodium tends to exchange more rapidly than potassium. In three instances the specific activity curves

deviate from the simple exponential behavior of a two compartment system. In the exchange of potassium in canine blood the deviation is caused by the presence of a rapidly exchanging fraction in the buffy coat cells. Such an effect does not account for the inhomogeneity of sodium exchange in human blood.

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