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Potassium and Water Distribution in Depression

By DAVID MURRAY SHAW and ALEC COPPEN

The ionic theory of cell excitability shows how impulses are generated, conducted and propagated by movements of ions between the cells and the extracellular fluid. It is known that changes in the concentration of sodium and potassium in either the extracellular water (E.C.W.) or the intracellular water (I.C.W.) may have a marked effect on the resting and action potentials of excitable cells. If affective disorders are manifestations of complex but reversible changes in brain excitability, then these in turn might be caused by alterations in the concentration of electrolytes within the cells of the central nervous system (C.N.S.). Although it is not possible to measure the distribution of electrolytes specifically in the C.N.S. in man, it is possible to measure their distribution in the body as a whole. In previous papers we have shown that residual sodium (intracellular plus a small quantity of bone sodium) is increased by 50 per cent. in depression (Coppen and Shaw, 1963) and by nearly 200 per cent. in mania (Coppen, Shaw, Malleson and Costain, 1965). The present paper shows that there are also abnormalities in the distribution of potassium, the other main cation determining cell excitability, in patients suffering from severe depression.

Methods

The distribution of water, sodium, potassium, and chloride was determined in depressed subjects before and after recovery from their illness. We employed an isotope dilution technique, using ^{24}Na, ^{82}Br, and tritium, and whole-body counting to estimate the total body potassium.

Patients and Timing of Investigations

The subjects were suffering from severe unremitting depression, diagnosed on a history of profound depression accompanied to a greater or lesser extent by other symptoms, such as feelings of guilt and unworthiness; suicidal thoughts; loss of energy, interest and concentration; depersonalization; insomnia; loss of appetite. Patients who had had electric convulsive therapy (E.C.T.) within one month, tranquillizing drugs or monoamine oxidase inhibitors within two weeks, and those suffering from physical illness, severe malnutrition, or dehydration, were excluded.

The normal ward diet was given, with supplements of 186 g. of "Complan" in 850 ml. of milk daily in three divided doses for two or three days before starting the investigation. The patients were kept up and about, and activity in the ward was encouraged, especially during the 24 hours of the investigation.

All the patients were treated by E.C.T., and initial studies were made a few days after admission and were repeated a minimum of six days after the last E.C.T.

Estimation of Total Body Potassium

Total body potassium was estimated at the Medical Research Council's Radiological Protection Service, Belmont, Sutton. The details of the method have been published elsewhere (Maycock, Terry, Vennart, and Wise, 1960), and involve counting body radioactivity due to ^{40}K for 60 minutes in a sensitive body-counter. Naturally occurring potassium contains 0·012 per cent. of the radioactive isotope of potassium ^{40}K. From a measurement of body radioactivity due to ^{40}K the total body potassium was estimated by comparison with a phantom model of the human body filled with known amounts of potassium chloride. The method gives results accurate to ± 260 mEq. of potassium.

Estimation of Total Body Water, Bromide Space, and Exchangeable Sodium

Radioactive isotopes were prepared by the Isotope Division of A.E.R.E. (Harwell) every second week from "specpure" Na_2CO_3 and "analar"

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NH_4Br. The $(^{24}Na)Na_2CO_3$ was neutralized with 0·1 N HCl and was made to 15 ml. with 0·5 per cent. (w/v) NaCl solution. Samples of the stock solutions were diluted to an activity of 5 μc./ml. at the time of administration of the isotope to the patient. A volume of 3 ml. of 0·02 N sodium thiosulphate was added to the solid $NH_4Br(^{82}Br)$ and the solution was made up to 15 ml. with 0·5 per cent. (w/v) NaBr solution. Aliquots of stock ^{82}Br solution were diluted as required to give an activity of 2·5 μc./ml. at the time of administration. Tritiated water was diluted to an activity of 50 μc./ml.

Volumes of 10 ml. were pipetted from each of the diluted solutions of ^{24}Na, ^{82}Br, and tritiated water into plastic dose-containers to give doses of 50, 25 and 500 μc. respectively. The mixed solutions and three washings of the container were given to the patients orally, through a straw, at 9.30 a.m. on the day of the test.

Pairs of 50-ml. plastic centrifuge tubes used for the blood samples were heparinized by the addition of 0·2 ml. of a 1 per cent. (w/v) solution of calcium heparin, 50 units/mg. To one of these tubes was added 0·2 ml. of a 5 per cent. (w/v) solution of sodium bromide, and both tubes were dried in an oven at 80°C.

For 23 hours after ingesting the isotopes all urine passed by the patient was collected in a plastic bottle. One hour later a "spot" sample was passed directly (in the case of female patients through a plastic funnel) into another plastic container. Then 40 ml. of blood was taken from an antecubital vein and the sample was divided between two centrifuge tubes. These were agitated gently and were spun immediately at 1,200 g. for five minutes. Plasma from the tube containing only calcium heparin was used for the estimation of the concentrations of sodium and potassium. The plasma containing heparin and carrier bromide was used for all the other determinations.

The sodium concentrations of the "spot urine" and plasma, and potassium concentrations of plasma were determined in duplicate by means of an EEL flame photometer.

^{24}Na and ^{82}Br were separated for counting with ion-exchange resins. Columns were prepared from glass tubing of 5·5 mm. internal diameter drawn out at one end to an internal diameter of 2 mm. This end was plugged with glass-wool. A 5-cm. length of small-bore rubber tubing was attached to the tapered end and a gate-clip was used to occlude the tubing.

The two resins used, "zeo-karb 225" (SCR 13) and "de-acidite FF" (SRA 69), were converted to their H^+ and OH^- forms respectively, and two columns of each were made for each estimation. The height of the columns was 25 cm. from the glass-wool plug, and each was washed through with six bed volumes of ion-free water. The two de-acidite FF columns were used for 13-ml. aliquots of the "23-hour-" urine and the "spot" urine samples, and the zeo-karb 225 columns were used for 13 ml. of the 23-hour urine and for 13 ml. of a 1 in 3 dilution of the plasma. To avoid "dilution" effects from the water in the column the gate-clip was opened to allow a very slow flow. When the water reached the top of the resin 7 ml. of the urine or diluted plasma was added to top of the column in 0·5-ml. amounts which were allowed to drain through to resin bed level and were discarded. The remainder of each aliquot (6 ml.) was passed through the columns and the effluent was collected.

Estimations of tritium were made on the "spot" samples and the "23-hour" urine. Before the test was repeated, a sample of urine was collected to measure the tritium remaining in the body from the previous test.

Tritiated water was extracted from the samples by distillation to dryness under reduced pressure and was collected in a "U" tube immersed in a freezing mixture of methanol and solid carbon dioxide.

All samples were counted for a minimum of 10,000 counts. Five-ml. samples containing either ^{24}Na or ^{82}Br were counted in a well scintillation counter. Tritium was estimated at room temperature, using a low-energy coincidence-counter. One-millilitre aliquots were pipetted into counting cuvettes and 14 ml. of liquid scintillator NE.220 (Nuclear Enterprises Ltd.) was added. The samples were kept in the dark overnight before being counted.

The calculation of the data and of the values derived from the data has been described by Veall and Vetter (1958).

Estimated Values		*Units*
Weight (Wt)		kg.
Total body water (T.B.W.)		l.
Distribution volume of bromine (DBr.)		l.
Exchangeable sodium (Na_E)		mEq.
Total body potassium (K_T)		mEq.
Concentration of electrolytes in plasma ($[Na]_{out}$ $[K]_{out}$ $[Cl]_{out}$)		mEq./l.
Derived Values	*Derivation*	*Units*
Extracellular water (E.C.W.)	DBr. × 0·9	l.
Sodium in extracellular space (Na_{out})	$[Na]_{out}$ × E.C.W.	mEq.

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Derived Values	*Derivation*	*Units*
Residual sodium (Na_R)	$Na_E - Na_{Out}$	mEq.
"Average residual sodium concentration" ($[Na]_R$)	Na_R/I.C.W.	mEq./l.
*Intracellular potassium (K_{In})	$K_T - K_{Out}$	mEq.
*Average intracellular potassium concentration ($[K]_{In}$)	K_{In}/I.C.W.	mEq./l.

Residual F factors (Predicted value − observed value)

*Unlike sodium, potassium is almost entirely intracellular and therefore residual potassium is termed K_{In} rather than K_R.

The variables we are most concerned to examine, total body and intracellular potassium, exchangeable sodium, residual sodium and E.C.W. are correlated with body weight and even more highly correlated with T.B.W. Moore, Olesen, McMurrey, Parker, Ball and Boyden (1963) and also Anderson (1963) have published extensive data on the distribution of sodium and potassium in normal subjects using techniques similar to our own and they give numerous regression equations relating exchangeable sodium and other variables to T.B.W. To analyse our data we have used these regression equations by employing a procedure proposed by Lindegård (1953) which has been utilized in a variety of anthropometric and psychosomatic investigations. This technique can be illustrated by considering total body potassium. Anderson gives a regression equation which enables the total body potassium of a normal subject to be predicted on the basis of his T.B.W. We applied this regression equation to our patients and calculated the difference between the "observed" and "predicted" values of total body potassium. This difference (using the convention introduced by Lindegård) is called residual F total body potassium (T.B.W.). This was determined for each patient for total body potassium and also for the other variables which are highly correlated with T.B.W. The resulting "residuals" were then treated as a series of variables and analysed statistically by conventional methods. We have compared the differences between the means of the various groups by using the "t" test. The regression equations used in this paper are listed in Table I.

Values for $[K]_{In}$, $[K]_{In}/[K]_{Out}$, I.C.W./E.C.W., etc. have been recalculated from the values for normal individuals published by Moore *et al.* (1963) using our own correction to DBr. to derive E.C.W.

Exchangeable potassium is usually slightly less than total body potassium estimated in a body counter (Remenchik and Miller, 1962; Coppen and Shaw, 1965). Since some of the normal data were based on exchangeable potassium we have converted all K_E figures to K_T by dividing by 0·95.

TABLE I

Regression Equations used in this Paper to Derive Residual F Factors

Regression equation	Correlation coefficient	Subjects Sex	Subjects Age-range	Source	Remarks
(1) $Na_E = 1{\cdot}013\ K_E - 635$	0·91	M		Moore, Olesen,	Equations (1) and (2)
(2) $Na_E = 0{\cdot}744\ K_E + 522$	0·87	F	20–60	McMurrey, Parker,	rearranged to give predicted K_E from Na_E.
(3) $K_E = 97{\cdot}41$ (T.B.W.) − 409	0·98	M & F		Ball and Boyden (1963)	All predicted K_E values converted to K_T by dividing by 0·95.
(4) $K_T = -6{\cdot}03$ (Wt) + 100·4 T.B.W.	—	M	—	Anderson (1963)	Other regression equations given by Anderson for predicting K_T gave very similar results to the one used.
(5) E.C.W. = 0·380 (T.B.W.) + 3·58	0·90	M & F	23–80	Moore *et al.* (1963)	Regression equation recalculated from original data using our own derivation of E.C.W. from DBr.
(6) $Na_E = 68{\cdot}10$ (T.B.W.) + 253	0·94	M & F	20–60	Moore *et al.* (1963)	

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TABLE II

Total Body Potassium and Other Values

Age (Years)	Sex	Weight (kg.)		T.B.W. (l.)		E.C.W. (l.)		I.C.W. (l.)		K_T (mEq.)		K_R (mEq.)		$[K]_{in}$ (mEq/l.)		$[K]_{out}$ (mEq./l.)		$\frac{[K]_{in}}{[K]_{out}}$		Na_E (mEq.)	
		D	R	D	R	D	R	D	R	D	R	D	R	D	R	D	R	D	R	D	R
60	F	58·4	58·3	31·9	38·6	15·7	14·6	16·2	24·0	2400	2330	2330	2260	144	94	4·6	5·1	31	18	3180	2530
47	M	81·5	83·9	48·8	52·2	19·7	20·6	29·1	31·6	3680	3760	3570	3660	123	116	5·4	5·1	23	23	3690	3810
62	F	58·2	61·5	28·2	33·0	13·2	12·4	15·0	20·6	1890	1820	1810	1760	121	85	5·2	4·7	23	18	2770	2410
64	F	52·7	56·5	33·8	32·1	15·4	16·4	18·4	15·7	3170	3040	3100	2960	169	189	4·5	4·7	37	40	2730	3030
51	M	57·1	56·5	39·6	39·5	15·9	16·7	23·7	22·8	3150	3260	3070	3190	130	140	5·0	4·4	26	32	2830	2890
76	M	57·2	57·6	34·3	37·5	15·6	15·6	18·7	21·9	2630	2890	2550	2800	137	128	5·0	5·2	27	25	3190	2750
63	F	49·0	51·3	30·5	30·9	15·1	14·6	15·4	16·3	2020	1970	1950	1890	127	116	4·7	5·2	27	22	2550	2350
59	F	85·5	84·8	39·4	38·2	16·3	18·6	23·1	19·6	2460	2760	2380	2670	103	136	5·1	4·6	20	30	3180	3370
55	M	91·8	90·7	50·8	45·3	21·9	21·2	28·9	24·1	3450	3100	3350	2990	116	124	4·8	5·0	24	25		
42	F	59·0	63·0	33·3	35·3	14·7	15·6	18·6	19·7	2860	3400	2790	3330	150	169	4·7	4·6	32	37		
68	M	61·7	64·6	41·7	41·8	18·5	20·1	23·2	21·7	3580	3810	3500	3720	151	171	4·3	4·4	35	39		
59	M	67·1	68·7	44·5	44·3	18·2	19·5	26·3	24·8	3630	3530	3540	3430	135	138	4·7	4·9	29	28		
29	M	67·6	70·3	42·3	47·6	18·4	19·3	23·9	28·3	3630	3680	3530	3590	148	127	4·6	4·6	32	28		
39	M	81·4		45·6		17·3		28·3		4140		4060		143		5·1		28			
49	F	66·4		30·8		13·2		17·6		2610		2550		145		4·6		32			
52	F	46·7		29·9		11·6	16·7	18·3		2530		2480		136		4·4		31			
42	M		60·5		36·2		16·7		19·5		2300		2220		114		5·0		23		

D = Depressed phase

R = After clinical recovery.

TABLE III

Mean Values in Depressed Patients and in Normal Subjects

Clinical State	Source of data	Mean age and range (yrs.)	Number	$[K]_{In}$ mEq./l.	$[K]_{In}/[K]_{out}$	Na_E/K_T
(A) Depressed	Coppen and Shaw (1963)	54·7 (29–76)	16	136	28·6	1·09*
(B) After recovery from depression	Coppen and Shaw (1963)	55·5 (29–76)	14	132	27·6	1·10†
(C) Normal subjects	Moore *et al.* (1963)	49·7 (23–84)	33	166	38·3	0·93
* 11 subjects † 10 subjects	Significance of differences between means		A vs. B	N.S.	N.S.	N.S.
			A vs. C	< ·001	< ·001	< ·005
			B vs. C	< ·001	< ·001	< ·001

It should be explained that we are using two similar terms with different meanings, but the two names are now well established conventions. One is "residual sodium" which is the residuum when sodium in the E.C.W. is subtracted from exchangeable sodium. The other is "residual F factor" and this is the difference between an observed value and that predicted from a given regression equation.

RESULTS

The main findings are shown in Table II. Table III gives some of the mean values for each group. The average total body potassium and intracellular potassium do not show any significant change during recovery from a depressive illness. The apparent intracellular potassium concentration and the average ratio of potassium concentration between cells and E.C.W. do not alter significantly with recovery. However the mean values for $[K]_{In}$ and the ratio, $[K]_{In}/[K]_{Out}$ in patients were significantly lower than the values seen in normal subjects. The mean ratio of Na_E/K_T (Table III) is high both in depressed subjects and in patients who have recovered from depression. The means for residual F factor K_T (T.B.W.) are low particularly after recovery which again emphasizes the relative lack of body potassium. (Table IV).

T.B.W. and Na_E are normal in depression (Coppen, Shaw, Malleson and Costain, 1965) but when total body potassium is assessed on the basis of these variables it is shown to be reduced in size. The mean ratio of I.C.W. to E.C.W. is 1·31 which is considerably higher than that found in normal subjects (1·04). This relative increase of I.C.W. is further illustrated by the negative residual F values for E.C.W. (T.B.W.) in Table IV. $[Na]_R$ is increased and the ratio $[Na]_{Out}/[Na]_R$ is decreased during depression (Table V). Both values return to normal after recovery.

DISCUSSION

In depressed subjects, both before and after recovery from their illness there is an apparent lack of intracellular potassium.

The partition of T.B.W. is abnormal, as these patients show a relative decrease in E.C.W. and an increase in I.C.W. This shift of water from E.C.W. to I.C.W. would tend to decrease intracellular potassium concentration further and to magnify the abnormality in body potassium found in these patients. For this reason the validity of the estimate of E.C.W. must be established.

The measurement of E.C.W. is based on the volume of distribution of bromine and it can be argued that there are disadvantages in using an ion to measure E.C.W. where there are electrolyte disturbances. However there are several reasons for thinking that the use of ^{82}Br to measure E.C.W. in depressed patients does not give rise to spuriously low figures:—

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TABLE IV

Residual F Values in Depressed and Normal Subjects

	Clinical State		Residual F Factors mean values K_T (T.B.W.) (mEq.)	E.C.W. (T.B.W.) (l.)	Na_E (T.B.W.) (mEq.)	K_E (Na_E) (mEq)
	(A) Depressed		−472	−1·74	+51	—
	(B) After recovery from depression		−728	−1·35	−133	−754
Significance of differences	Between means of predicted and observed values	(A)	<·005	<·001	N.S.	—
		(B)	<·001	<·001	<·05	<·001
	Between means of depressed patients and means after recovery	A vs. B	N.S.	N.S.	N.S.	—

1. All the technical errors which include adsorption losses of isotope, dilution of the ^{82}Br in the resin columns, etc., would tend to result in an overestimate of the volume of distribution of bromine. If there are no technical reasons for low E.C.W. figures then the only remaining way in which this might have happened would be if there were greater than normal exclusion of ^{82}Br from erythrocytes and body cells. This possibility can be excluded with reasonable certainty (see appendix).
2. Considering only patients who have recovered from depression (Table V) and assuming that the whole of Na_R is intracellular then the mean ratio of sodium across the cell membrane is 8·06. This figure is not significantly different from the normal subjects and is not much lower than normal figures for the ratio of sodium across cell membranes in mammalian tissues. If E.C.W. were larger than suggested by our data, Na_{Out} would be increased, Na_R would be correspondingly smaller and since $[Na]_{Out}$ is unaltered the ratio of $[Na]_{Out}/[Na]_R$ would be increased. Sodium is moved across the cell membrane up a steep electrochemical gradient and it is extremely unlikely that the cells of depressed subjects after recovery perform this task better than normal subjects.

It seems likely therefore that E.C.W. derived from the volume of distribution of bromine is a reliable measure of the extracellular space in

TABLE V

Means of Sodium and Water Distribution in Depressed and Normal Subjects

Clinical State	Source of data	Number	Mean age	I.C.W./E.C.W.	$[Na]_R$	$[Na]_{out}/[Na]_R$	T.B.W. (l.)	E.C.W. (l.)
Depressed	Coppen and Shaw (1963)	23	55·7	1·31	28·7	5·66	35·1	15·2
After recovery from depression	Coppen and Shaw (1963)	19	55·7	1·31	21·3	8·06	36·7	15·9
Normal subjects	Moore *et al.* (1963)	33	49·7	1·04	20·8	7·39	32·7	16·0
	Significance of differences between means			N.S.	<·05	<·0		
				<·001	<·001	<·005		
				<·001	N.S.	N.S.		

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depressed subjects and that it is valid to compare the intracellular potassium of our patients with values obtained in normal subjects using similar techniques.

Since the bulk of the body cell mass is muscle, this tissue must be implicated in the deficiency of potassium, but there is no direct evidence that the brain is involved. There is indirect evidence from neurophysiological studies which we discussed in our previous papers (Coppen and Shaw, 1963; Coppen, Shaw, Malleson and Costain, 1965) that brain excitability is altered in depression and this could have arisen from alterations in ionic equilibria.

If it is assumed that the changes in electrolyte distribution involve all parts of the body including the C.N.S. then the consequences must be considerable. The resting potential of cell membranes is given by the Nernst equation:—

$$E = \frac{RT}{F} \ln \frac{[K]_{in}}{[K]_{out}} \text{ millivolts}$$

Normal individuals would have a mean resting potential of −97 millivolts and the group who have recovered from depression a resting potential of −89 millivolts. The difference, 8 millivolts, is similar in magnitude to those excitatory post synaptic potentials which are large enough to initiate action potentials.

The increase in residual sodium, which probably represents an increase in intracellular sodium, could greatly reduce the action potential of excitable cells. The action potential approaches the equilibrium potential for sodium and is given by the Nernst equation:–

$$E = \frac{RT}{F} \ln \frac{(Na]_{out}}{[Na]_{in}} \text{millivolts}$$

If we assume that residual sodium is all intracellular then depressed patients would have a mean action potential 7 millivolts below the mean for normal individuals.

Thus our work on the distribution of electrolytes in depression has revealed three changes:—

(*a*) a considerable increase in residual sodium, which returns to normal with recovery.

(*b*) a decrease in total body potassium and in the concentration of potassium in the cells,

(*c*) a relative increase in I.C.W. and decrease in E.C.W.

Neither the deficit in potassium nor the abnormal partition of T.B.W. between I.C.W. and E.C.W. is altered by the process of recovery.

Thus during a depressive illness the changes in electrolyte distribution would tend to reduce both the resting and action potentials of excitable cells. How such changes in cell function would affect the integrated activity of the brain is impossible to say at our present stage of knowledge.

Summary

Potassium and water distribution were examined in patients during and after a depressive illness. There was a relative deficiency of total body potassium, and the concentration of intracellular potassium was low when compared to values obtained on normal subjects. It was found that these patients showed a relatively increased I.C.W. and decreased E.C.W. These abnormalities showed no change with clinical recovery.

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Appendix

Estimates of E.C.W. are obtained by multiplying the distribution volume of bromine by 0·9. This is necessary because bromine is not confined to the extracellular space but in part penetrates into the cells. If E.C.W. is underestimated in depressed patients then more bromine must be excluded from the cells than in normal individuals. The only other possible cause of spuriously low E.C.W. values is incomplete equilibration and this can be discounted.

The main loss of bromine ion from E.C.W. is into red cells where there is a Gibbs-Donnan equilibrium:–

$$\frac{[OH]_{In}}{[OH]_{Out}} = \frac{[HCO_3]_{In}}{[HCO_3]_{Out}} = \frac{[Cl]_{In}}{[Cl]_{Out}} = \frac{[Br]_{In}}{[Br]_{Out}}.$$

$[Cl]_{Out}$ and $[Cl]_{In}$ are normally about 105 mEq./l. and 74 mEq./l. respectively, and therefore these ratios have a value in the region of 0·7. Suppose there were large electrolyte changes and half the red cell chloride were lost. Assuming an E.C.W. of 15 litres and a red cell water of 1·5 litres this would give an

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apparent decrease of E.C.W. of 3·5 per cent. Our estimates of $[K]_{In}$ in depressed patients although increased would still be significantly lower than normal. However since the Gibbs-Donnan equilibrium applies to the hydroxyl and bicarbonate ions this would imply a change in acid-base balance in the blood, and there is no evidence for this in depression (Challenger and Leyton, 1964).

There is a small loss of bromine into other cells most of which are muscle fibres. Muscle fibres obey the Gibbs-Donnan equilibrium so that:—

$$\frac{[K]_{In}}{[K]_{Out}} = \frac{[Cl]_{Out}}{[Cl]_{In}}.$$

This ratio is about 60 : 1 in normal muscle. An increase in this ratio is unlikely in depression because plasma potassium concentration is normal and the potassium content of the body is low.

Finally, about 2 per cent. of bromine is in the gastro-intestinal tract (Veall and Vetter, 1958). It is unlikely that this minute fraction is reduced further.

We conclude that the estimates of E.C.W. are valid and that differences in the distribution of bromine do not account for the abnormal partition of T.B.W. and low intracellular potassium values observed in depressed patients.

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