CCIII. REMOVAL OF BROMINE FROM THE BLOOD IN CASES OF MENTAL DISORDER.

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ZONDEK AND BIER [1932; 1933] have pointed out that in certain cases of mental disorder (particularly of the manic-depressive type) the blood-bromine is usually considerably lower than normal. Unfortunately they used a method of bromine estimation which is subject to severe criticism and hence, although their conclusions may be correct, the work requires repetition with a sound method of bromine estimation. Work in this laboratory¹, using Yates's method of bromine estimation [1933], has made it clear that the bromine of blood varies very greatly among cases of mental disorder, but that variation occurs also among normal subjects, particularly women (compare also Kuranami [1932] and Guillaumin and Merejkowsky [1933]).

The authors have made an attempt, in the work about to be described, to analyse some of the factors which may contribute to the variations in blood-bromine.

It seemed possible that the rates at which tissues remove bromine from blood may vary from patient to patient. Small amounts of bromine are normally taken in the food [Damiens and Blaignan, 1932]), but this is subject to such wide fluctuation that quantitative investigation is difficult. We have therefore given patients and normal subjects, intravenously and orally, known quantities of bromide and followed the rates at which bromine disappeared from the blood after reaching its maximum value.

Removal of bromine from the blood.

A number of patients were given 1 g. of sodium bromide dissolved in 50 ml. of saline by intravenous injection. The injections were made in the morning, 2 hours after the patients had breakfasted. All patients were kept in bed during the next 5 hours. The first sample of blood (10 ml.) was taken less than 5 minutes before the injection. The bromide solution was then injected, and samples of blood were withdrawn for bromine estimation at intervals of 1, 2 and 5 hours from the time of injection. Analyses were also made 1, 4 and 7 days after the time of injection. The patients during the whole of the experimental period were on their normal diet, and received no medicinal treatment during this period.

Results with 8 patients and 3 normal cases are recorded in Table I.

The following facts are noteworthy:

(1) The calculated blood-bromine immediately after injection of the bromide, assuming even distribution throughout the blood, is of the order 15–20 mg./100 ml. The value of blood-bromine found 1 hour subsequently was of the order

¹ By Yates and Hennelly (to be published shortly).

Table I.

Name	Diagnosis	Weight kg.	Initial blood- bromine mg./100 ml.	Blood-bromine (mg./100 ml.) Time in hours after injection						Blood- bromine immedi- ately following injection (calc. *) mg./100ml.	% drop in blood- Br in 1 hr.	% drop in blood- Br in 24 hrs.	Urine (first 24 hours)		
				1	2	5	24	96	168				Vol. (ml.)	Br mg./ 100 ml.	Total bromine mg.
Y.	Normal	66.6	0.95	2.72	3.00	2.70	1.64	1.31	1.20	15.3	88.5	95.2	900	2.38	21.5
F.	Normal	65.7	1.46	2.12	2.45	2.77	1.76	1.32	1.28	15.4	91.5	98.1	1470	1.25	18.4
P.	Normal	56.7	0.83	3.53	2.95	3.22	2.61	1.45	1.22	17.8	88.0	90.1	1710	2.53	43.3
J. R.	Manic-depressive	79.7	0.59	2.48	2.32	1.87	2.86	1.40	0.85	12.7	86.2	82.4	1800	4.82	86.8
C. E.	Dementia paranoides	49.0	0.52	4.81	4.00	4.38	3.88	—	2.08	20.6	78.2	82.6	1050	3.61	39.7
O. K.	Hebephrenia	69.8	0.19	3.50	2.93	2.80	2.40	—	1.90	14.5	81.2	84.9	530	0.63	3.3
S.	Dementia paranoides	64.3	0.41	3.96	3.92	3.76	3.34	—	1.96	15.6	77.4	87.4	1090	1.64	17.9
P. T.	Melancholia	59.4	0.29	3.66	3.40	3.08	2.78	—	1.78	17.0	81.6	85.2	1260	0.42	5.3
N.	Dementia paranoides	53.6	0.14	3.80	3.48	3.22	2.78	—	1.83	18.8	82.2	86.3	730	1.19	8.7
M.	Paraphrenia	50.4	1.14	3.66	3.46	2.10	1.54	—	1.47	20.0	80.3	98.0	1180	1.08	12.7
O. B.	Catatonia	53.1	1.17	3.78	3.28	2.40	1.30	—	1.26	18.9	89.7	99.3	460	2.87	13.2

* Calculated on the basis of blood weight = 1/13 body weight.

3-4 mg./100 ml. Examination of column 10 will show that the percentage drop in blood-bromine during the one hour from the time of injection is very nearly the same in all cases examined—both normal and mentally abnormal.

It is evident that there is a rapid diffusion of bromide from the blood into the tissues, the velocity of this diffusion, at any rate in the initial stages, being, so far as we can ascertain, independent of the mental state.

(2) Although the initial blood-bromine (*i.e.* before injection of bromide) differs very greatly among the 11 cases studied, the values of blood-bromine one week after the injection of bromide bear but little relation to the initial values and are not very greatly dissimilar from each other. Examination of column 11 indicates that the percentage drop in blood-bromine 24 hours after the time of injection is much the same in all cases. This can be seen more clearly in Table II, where results with the two groups of patients (A, those with normal

Table II.

	Av. blood-bromine (mg./100 ml.) (initial)	Av. fall % in blood-bromine		% of total bromine in urine in 24 hrs.
		0 to 1 hr.	1 to 24 hrs.	
A	1.13	89.3	5.1	3.64
B	0.36	83.1	5.2	2.99

initial values of blood-bromine between 0.83 and 1.46 mg./100 ml. and B, those with low initial values) are summarised.

The maximum amount of Br in the urine after 24 hours was found to be only 86.8 mg., *i.e.* 11 % of the total Br injected.

It seems evident that the rate of removal of bromine from the blood is largely independent of the mental state, and low values observed are clearly not due to greater rates of removal from the blood into the tissues.

The variations in blood-bromine after oral dosage with sodium bromide (4 g. in 200 ml. of water) are shown in Table III.

Table III. *Blood-bromine after oral doses of sodium bromide (4 g.).*

Name	Diagnosis	Initial value prior to bromide inges- tion	Blood-bromine (mg./100 ml.) Time in hours after oral dose								
			1	2	4	26	96	120	264	336	504
E. Y.	Normal	0.96	2.02	4.72	—	5.8	4.17	—	—	1.54	—
C. F.	Dementia	0.90	—	21.4	33.4	33.0	—	25.8	—	18.8	—
G. E.	Dementia	0.92	—	12.7	15.6	14.9	9.0	—	4.6	—	1.35
S. K.	Oligophrenia	0.81	—	4.71	3.75	1.35	—	—	0.92	—	—
J. H.	Epileptic	0.72	—	5.00	5.72	5.35	—	1.8	—	1.05	—
S.	Manic depressive	2.15	—	—	11.1	11.9	—	6.85	—	—	—
P. J.	Dementia	1.47	—	16.9	—	—	—	—	—	—	—
W.	Melancholia	0.67	—	9.8	9.9	8.95	—	—	—	3.85	—
D. O.	Hebephrenia	0.20	—	5.90	8.4	6.6	—	3.75	—	—	—
J. R.	Manic depressive	0.62	5.62	5.22	5.90	4.96	—	—	3.55	—	1.80

(3 g. NaBr given)

The whole picture is much more complicated than that seen after intravenous injection—there are differences between the patients, doubtless in their rates of absorption of the relatively large dose of bromide into the blood-stream [compare Tixopéus, 1930; Zondek, 1933; Baur and Oppenheimer, 1922].

It is important to note, however, that the patients with low initial blood bromine values show a decided increase in blood-bromine, our figures lending

little support to the supposition that patients with low initial blood-bromine values owe such low values to an inability to absorb bromine into the bloodstream.

Distribution of bromine in the tissues.

In order to obtain some further details of the way in which bromine distributes itself in the animal organism we have made a complete analysis of a rabbit killed after intravenous treatment with 39 mg. (0.015 g./kg.) sodium bromide. The highest concentrations were found in the blood (2.85 mg./100 ml.), heart (2.80 mg./100 ml.), kidney (2.03 mg./100 ml.), spleen (1.90 mg./100 ml.) and stomach (1.40 mg./100 ml.). It is significant that, as in other investigations with higher concentrations of bromide, this halogen is not found concentrated largely in one particular organ, but is found distributed generally throughout the organism. Ellinger and Kotake [1911] consider that the subcutaneous tissues and liver are the largest bromide depots, while Toxopéus [1930] finds that about one-third of the bromide given to dogs by the mouth is associated with muscular tissue, further large amounts being found in the skin and gastro-intestinal system [*cf.* also Purjez *et al.*, 1933]. The concentration of bromide in these organs does not however differ very considerably from that in the other organs.

Experiments on human subjects have hitherto been confined to studies of the blood, cerebrospinal fluid and urine. Early investigation showed however that bromide replaces chloride in the gastric secretions [Nencki and Shoumow-Simanowsky, 1894], and indicated the possibility that the intestinal system could accumulate fairly large proportions of injected bromide. We were led therefore to investigate the distribution of bromine between blood and gastric juice in patients without previous bromide treatment.

Bromide in the gastric juice.

Specimens of resting gastric juice and blood were taken from a series of 12 psychotic patients following a 12-hour fast. Estimation of the bromine content gave the following results (Table IV).

Table IV.

Patient	Blood-Br mg./100 ml.	Gastric Br mg./100 ml.	Ratio. $\frac{\text{Gastric Br}}{\text{Blood-Br}}$
F. H.	0.42	1.10	2.62
H. R. (1)	0.54	1.87	3.45
O. K.	0.57	1.12	2.00
L. T.	0.60	1.73	2.88
H. R. (2)	0.66	1.46	2.21
A. R.	0.78	1.06	1.36
A. M.	0.90	0.80	0.89
G. M.	1.09	1.03	0.95
H. B.	1.14	0.24	0.21
G. G.	1.15	0.74	0.64
J. G.	1.26	0.62	0.49
J. T.*	9.0	20.0	2.22
P. S.*	10.1	20.9	2.05

* These patients had had previous bromide treatment.

The following points appear clear:

The bromine content of gastric juice is high and often exceeds that of blood.

The distribution of bromine between blood and gastric juice tends to favour blood at normal blood-bromine concentrations (0.7 to 2.0 mg./100 ml.).

When the blood-bromine falls lower than this normal level the distribution ratio rises in favour of gastric juice.

A possible explanation for the variation in the levels of blood-Br is thus suggested, the inverse relationship between the amounts of Br in blood and gastric juice indicating the possibility that a low blood-bromine level may result from a hypersecretion of bromine into the gastric juice.

In confirmation of this a study of 4 patients following a standard Rehfuess test meal (consisting of 600 ml. of thin gruel containing 0.08 mg./100 ml. Br administered after a 12-hour fast), showed that gastric bromine increases from 0.1 mg./100 ml. to values ranging from 0.78 to 1.25 mg./100 ml. Moreover the administration of such a meal to two patients showed that blood-bromine fell steadily during digestion (see Table V). A similar although very much smaller effect is observed with chloride [Peters and Van Slyke, 1931].

Table V.

Patient A		Patient B	
Time (mins.) after giving test meal	Blood-bromine mg./100 ml.	Time (mins.)	Blood-bromine mg./100 ml.
-45	1.01	-5	0.80
0	1.08	0	—
45	0.99	50	0.85
80	0.83	95	0.76
120	0.95	125	0.63
150	0.77	175	0.59

These results indicate therefore that gastric secretion plays some part in controlling the level of bromine in the blood, and that the interpretation of variations in blood-bromine [*cf.* Kuranami, 1933; Ewer, 1932] must include a consideration of this fact.

SUMMARY.

1. The rate of removal of bromine from the blood, after intravenous injection of sodium bromide, is independent of the mental state. Variations in the initial blood-bromine levels, found both in normal and mentally abnormal cases, cannot be attributed to differences between the rates of removal of bromine from the blood into the tissues.

2. After oral ingestion of sodium bromide, the blood-bromine rises markedly in all patients, independently of the mental state. Low blood-bromine levels found in certain psychotic patients cannot therefore be ascribed to lack of absorption of bromine into the blood-stream.

3. Bromine may appear in the gastric juice in concentrations greater than that in the blood.

4. During the process of digestion blood-bromine falls and the bromine in gastric juice rises. It is suggested that secretion of bromine into the gastric juice plays some part in determining the normal level of blood-bromine.

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