# BLOOD BROMINE IN THE PSYCHOSES.

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EARLY investigators differed widely in their estimations of the bromine content of normal blood (1, 2), and it was not until the development of a refined technique by Bernhardt and Ucko (3) that it was generally recognized that blood bromine varied around 1 mgrm. %. These authors gave a range of 1·0 to 1·6 mgrm. %. Their studies, however, were not extensive. During 1931–3 Zondek and Bier (4, 5, 6) published the results of a series of investigations into the bromine content of the blood of normal and psychotic patients. From a study of 150 mentally normal patients they considered that blood bromine usually varied between 0·8 and 1·0 mgrm. %, a range later extended to 0·73–1·10 mgrm. % as a result of further study. In a large number of psychotics examined by them, values lying within these limits were found with the notable exception that 85%–90% of 60 cases of endogenous manic-depressive psychoses gave figures 40% to 60% below their normal levels (Zondek, 1933) (6). These low figures appeared only to be associated with this psychosis, although of the 16 cases of schizophrenia examined by them, 5 gave figures lower than the normal. They stated that in these 5 cases the mental picture was characterized by more or less marked depression, and they considered the possibility of their ultimately turning out to be manic-depressive in character. In a later paper, three examples are cited of low blood bromine associated with organic brain disease, and thought to be due to interference with a bromine-regulating centre in the brain. The low values found in manic-depressive psychoses were shown to be independent of the phase, and it was stated that values in general were not subject to seasonal variations, to menstrual fluctuations, or to alterations due to variable salt intake.

The case-reports of Uhlman (7), Ewer (8) and Schneider (9) tended to confirm these general findings.

Klimke and Holthaus (10) state that in their experience the normal range differs little from that of Zondek and Bier (0·89 to 1·11 mgrm. %). They found low values associated with delirium tremens as well as with schizophrenia and reactive depression. No cases of manic-depressive psychoses are cited. They concluded that during a period of unrest there is a close parallelism between

the drop in blood bromine and the rise in vasomotor excitability, excitement with agitation lowering the blood bromine in every case irrespective of diagnosis.

Sacristan and Peraita (11) made investigations on 23 female psychotics (ages 44–69) in the Madrid Hospital for sleeping sickness, and found values ranging from 0·16 to 0·68 mgrm.% in 13 cases whose mental states were classified either as melancholia, mania or hypomania. Values for other psychotics ranged from 0·72 to 1·9 mgrm.%. In a further paper (12) they state that the bromine figures return to normal when the clinical picture indicates improvement. Kuranami (13) found the blood bromine ratio low (0·51 to 0·67 mgrm. %) in normal Japanese. His studies of two women showed wide fluctuations, values being low prior to menstruation and rising rapidly to a maximum during the next two days.

The method used by all these investigators in their estimations was that of Pincussen and Roman (14). This method has not a very sound theoretical basis, and since its inception has been subject to considerable technical criticism. While here not directly concerned with a discussion on analytical technique, it is worthy of note that losses of bromine have been reported in all stages of the oxidation and extraction processes (15, 16, 17), while partial interference of chloride as chlorine renders the bromine recovery higher than is to be expected. Accordingly the results which have been described using this procedure should be regarded with considerable uncertainty until confirmed by independent and more accurate methods.

Urechia and Retezeaunu (18, 19), using a method which is not capable of very exact refinement, found themselves in general agreement with Zondek. They observed low values in melancholia *per se*, and in the manic-depressive psychosis.

Guillaumin and Merejkowsky (20, 21), using a modification of the method of Bernhardt and Ucko (details of which have not been published), found in a study of 200 mentally normal patients suffering from chronic physical diseases, such as rheumatism, nephritis, cirrhoses, etc., a variation in values of from 0·2 to 2·0 mgrm. %. They consider their results to constitute a serious criticism of those of Zondek and Bier, and state that blood bromine lower than 0·6 mgrm.% can be found in other than depressed states, and cannot in itself be used as a diagnostic label.

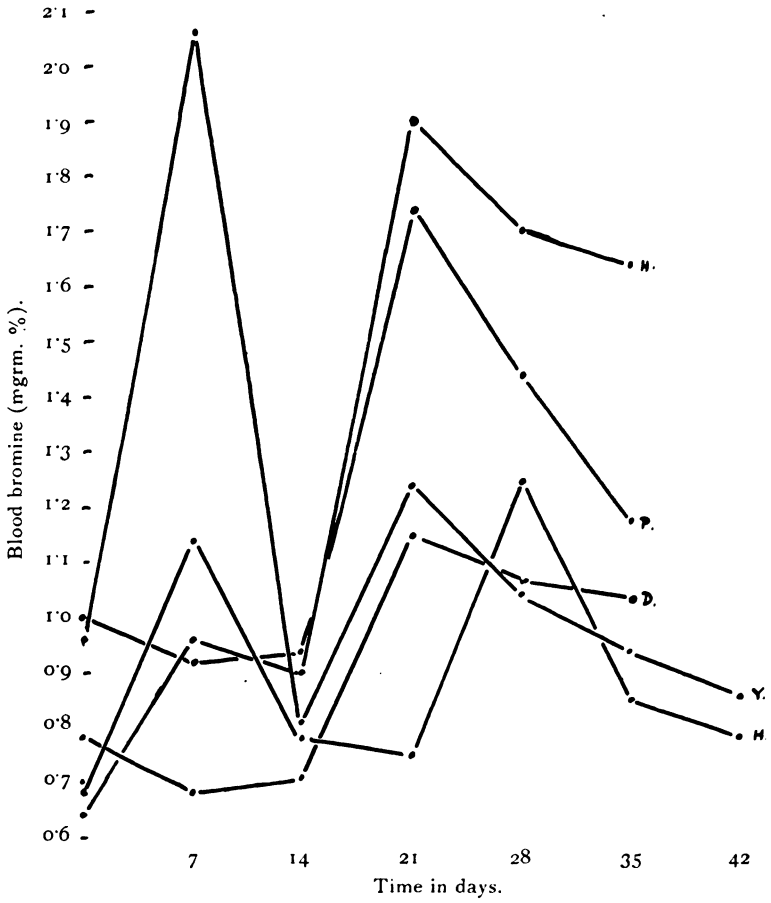
During the past year we have investigated the blood bromine of normal and psychotic people resident in the Cardiff City Mental Hospital. The method employed, developed by one of the authors, was shown to have an accuracy of at least 0·05 mgrm.% (22). In view of the importance so clearly to be attached to the reliability of the method, we would point out that the general principle involved in the estimation (viz., selective oxidation of bromide to bromine with chromic acid and removal of the latter by an air stream) has been utilized since 1897 by many investigators for the examination of large quantities of bromine in blood, while, with but slight modifications, its use has been

recommended by two other independent investigators (23, 24) for estimations down to as low as 0·02 mgrm. % of bromine.

TECHNIQUE OF METHOD EMPLOYED.

Take 5 c.c. of fresh oxalated blood and lyse with 35 c.c. of water for 15 minutes. Add 5 c.c. of 10% sodium tungstate and allow to stand for 30 minutes. Now add 10 c.c. of 2/3 N. sulphuric acid (5 minutes), centrifuge at 3000 revs. per minute

GRAPH I.—*Variation in Blood Bromine (Normal Male Staff).*




for 20 minutes, and decant off through a cotton-wool filter. Take an aliquot part (35 c.c.) of the filtrate, add 2 c.c. of 25% potassium hydroxide, and evaporate to dryness in a nickel crucible on a water-bath (1 hour). Ignite in an electric oven for 20 minutes at 500°. Cool and add 3 c.c. of water. Transfer the solute to a 50 c.c. Erlenmeyer flask. Wash the crucible thoroughly with two 2 c.c. portions of water, making the total volume in the flask 7 c.c. ± 0·1 c.c.

Cool the flask under running water and add very carefully, drop by drop, 2·5 c.c.

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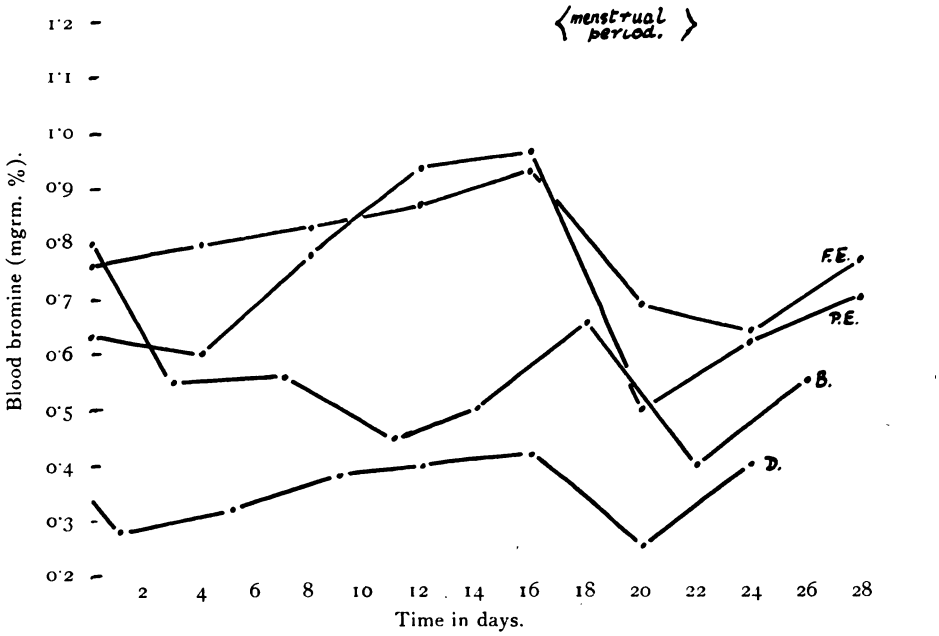
of concentrated sulphuric acid (the amount should be varied according to the strength of the acid; the specimen used in this work was 36·0 N.). Now add to the cold solution 4 c.c. of a chromic-sulphuric acid mixture consisting of 20 grm. of chromic oxide (halogen-free) dissolved in 40 c.c. of 36 N. sulphuric acid in 120 c.c. of distilled water. This mixture should be allowed to run all over the inside of the flask. Wipe the top of the flask, and remove the bromine formed by means of a stream of purified air into 1 c.c. of 10% potassium iodide solution containing 4 drops of 0·5% starch solution (3–5 hours). The temperature of the oxidation mixture should be maintained at 20° ± 1° C. Titrate the iodine formed with N/1000 thiosulphate from a microburette.

GRAPH II.—*Variation in Blood Bromine* (*Female Nurses*).




The results which we have obtained can, for convenience, be classified and discussed under the following heads: Normal range and variation of blood bromine; blood bromine in psychotics; variation of bromine during changes in mental state; the physiological basis for blood bromine variations.

## NORMAL RANGE AND VARIATION OF BLOOD BROMINE.

Our studies have shown a variation of from 0·6 to 2·0 mgrm.% for normal males. While a considerable proportion of these (60%) have values lying between the arbitrary limits fixed by Zondek, the variation in the blood bromine of individual cases over regular weekly periods, often amounting to 100%, is so considerable that we feel that little significance can be attached to the

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determination of single values of blood bromine. After a series of investigations of the blood bromine of four volunteer female nurses every four days for five weeks, we found at the lower levels an even wider range of variation for females, values as low as 0·25 mgrm.% being found. It appeared, therefore, that any significant relationship to be found between the blood bromine and the mental condition would be more easily observed among male patients, and our subsequent investigations have accordingly been confined to this group. Observations during the menstrual cycle showed high values towards the end of the premenstrual phase, but without further extensive investigation we are inclined not to exclude the possibility that this parallelism is fortuitous.

## BLOOD BROMINE IN THE PSYCHOSES.

The results of our investigations under this heading may be summarized in tabular form as follows:

| Mental classification. | Number of estimations. | Number of cases. | Number of cases with average below 0·7. | Blood bromine in mgrm.%. 0–0·7. | 0·7–1·1. | 1·1–2·0. |
|---|---|---|---|---|---|---|
| Normal | 44 | 11 | 0 | 3 | 28 | 13 |
| Oligophrenia | 22 | 4 | 1 | 10 | 11 | 1 |
| Psychoneurosis | 4 | 4 | 0 | .. | 1 | 3 |
| Organic dementia | 6 | 5 | 0 | .. | 3 | 3 |
| Schizophrenia: | | | | | | |
| (*a*) Dementia simplex | 6 | 2 | 1 | 3 | 2 | 1 |
| (*b*) Hebephrenia | 27 | 6 | 4 | 14 | 9 | 4 |
| (*c*) Catatonia | 13 | 6 | 2 | 7 | 5 | 1 |
| (*d*) Dementia paranoides | 19 | 6 | 3 | 6 | 6 | 7 |
| Paraphrenia | 3 | 3 | 1 | 1 | 1 | 1 |
| Manic-depressive psychosis | 36 | 7 | 5 | 27 | 6 | 3 |
| Involutional melancholia | 3 | 2 | 2 | 2 | 1 | .. |
| Total numbers | 139 | 45 | 19 | 70 | 45 | 24 |

It is quite evident that low values for blood bromine are not exclusive to manic-depressive patients, cases of low blood bromine having been found in all types of schizophrenia, in paraphrenia, in oligophrenia and in involutional melancholia. Nor do all manic-depressives have low values. The cases amongst the schizophrenic group which showed low values were none of them depressed. In most of the groups where low values were observed we made an intensive study of the variation in blood bromine of at least one patient at regular intervals of four to seven days for five weeks. The maximum variations observed were as follows:

| | | Average value. |
|---|---|---|
| Oligophrenia . . . . . | 0·22 to 0·80 . | 0·39 |
| | 0·74 ,, 0·98 . | 0·88 |
| Dementia simplex . . . . | 0·50 ,, 0·80 . | 0·63 |
| Hebephrenia . . . . . | 0·35 ,, 1·36 . | 0·73 |
| | 0·28 ,, 0·91 . | 0·58 |
| Dementia paranoides . . . | 0·50 ,, 1·36 . | 0·84 |
| | 0·68 ,, 2·35 . | 1·22 |
| Manic-depressive . . . . | 0·23 ,, 1·24 . | 0·58 |
| | 0·51 ,, 0·77 . | 0·60 |
| | 0·42 ,, 1·01 . | 0·57 |

## Variation of Bromine during Changes in Mental State.

With a view to discovering if there was any correlation between changes in mental state and variation in blood bromine, we followed up selected cases in different phases of their disorder for periods sufficiently long to justify the conclusion that it is impossible to correlate changes in blood bromine with any clinical changes, or vice versa. Below we give evidence in support of this contention.

Case 1.—S. H—, æt. 69. A manic-depressive of 23 years' standing, whose illness is characterized by frequent attacks of depression and elation, with short intervening periods of comparative normality. In his depressed phases (i) he is morose, solitary and practically mute, whilst in his manic phases (ii) he is excited, impulsive, interfering and voices grandiose delusions.

| Date. | Blood bromine in mgrm. %. | Mental state at date of examination. |
|---|---|---|
| 4.iv.33 | 0·23 | Phase I (depressed. |
| 20.iv.33 | 0·75 | ,, II (manic). |
| 30.v.33 | 0·23 | ,, I. |
| 5.x.33 | 0·50 | ,, II. |
| 15.xi.33 | 0·47 | ,, II. |
| 5.ii.34 | 0·48 | ,, II. |
| 16.ii.34 | 0·82 | ,, II. |
| 23.ii.34 | 0·41 | ,, I. |
| 21.iii.34 | 0·57 | ,, I. |
| 28.iii.34 | 0·43 | ,, I. |
| 4.iv.34 | 0·62 | ,, I. |
| 13.iv.34 | 0·52 | ,, I. |
| 20.iv.34 | 1·24 | ,, I. |
| 28.iv.34 | 0·85 | ,, I. |

There were no normal periods during these tests. On each occasion the patient showed evidence of being under emotional tension.

Case 2.—D. O'K—, æt. 24. A hebephrenic of some 3 years' standing, whose disorder is characterized by changes of phase, which can be divided into (1) periods during which he is quiet, solitary, manneristic, childishly inconsequent, a good worker and an inmate of a female-nursed ward (Phase I), and (2) periods during which he becomes very hallucinated, noisy and destructive, often impulsive and

violent, given to posing and attitudinizing and requiring nursing observation by male staff (Phase II).

| Date. | Blood bromine in mgrm. %. | Mental state at date of examination. |
|---|---|---|
| 7.ix.33 | 0·19 | Phase I. |
| 16.ix.33 | 0·19 | ,, I. |
| 6.xi.33 | 0·79 | ,, I. |
| 23.iii.34 | 0·51 | ,, I. |
| 27.iii.34 | 0·35 | ,, I. |
| 3.iv.34 | 1·36 | ,, II. |
| 10.iv.34 | 1·00 | Quieter, but still uncertain and unreliable. |
| 14.iv.34 | 0·57 | Phase II. |
| 18.iv.34 | 1·68 | ,, I. |
| 25.iv.34 | 1·03 | ,, I. |
| 1.v.34 | 0·54 | ,, II. |
| 14.v.34 | 0·57 | ,, I. |

CASE 3.—J. R—, æt. 56. A manic-depressive who has been in and out of mental hospitals for the past 30 years. Finally settling in Cardiff, he was admitted to the City Mental Hospital, first in 1928, and since then on two other occasions, the last being in 1932. His psychosis shows itself in frequent fluctuations between mania and melancholia. These rapidly alternate with occasional short intervening periods during which there is no affective disturbance. The intervening periods are becoming progressively shorter, and within the past 18 months he has had only 4 days of a normal phase (25.i.34 to 29.i.34), during which he was free from emotional tension. In his manic phases he is extremely aggressive, noisy, abusive and obscene, and spends his days swaggering and strutting round voicing various grandiose delusions. When depressed he is solitary, uncommunicative and retarded, uninterested in his surroundings and pessimistic regarding his future.

| Date. | Blood bromine in mgrm. %. | Mental state at date of examination. |
|---|---|---|
| 5.x.33 | 0·77 | Maniacal. |
| 6.xi.33 | 0·51 | Depressed. |
| 25.i.34 | 0·56 | Normal phase, free from emotional tension. |
| 1.ii.34 | 0·56 | Depressed. |
| 5.ii.34 | 0·59 | Maniacal. |
| 13.ii.34 | 0·54 | ,, |
| 21.ii.34 | 0·62 | ,, |
| 1.iii.34 | 0·58 | ,, |

CASE 4.—J. A. N—, æt. 25. A depressed præcox of 3–4 years' duration, whose psychosis is characterized by somatopsychic delusions, dull apathy, seclusiveness and lack of interest in his surroundings. There was no change in his mental state throughout the whole period of the estimations. He was depressed and hypochondriacal, with ideas of bodily and facial distortion; was completely out of touch with reality and preoccupied with his delusions.

| Date. | Blood bromine in mgrm. %. | Mental state at date of examination. |
|---|---|---|
| 18.viii.33 | 0·14 | |
| 21.iii.34 | 1·06 | |
| 28.iii.34 | 0·89 | |
| 4.iv.34 | 0·74 | As above. |
| 13.iv.34 | 0·50 | |
| 20.iv.34 | 1·36 | |
| 28.iv.34 | 1·20 | |

CASE 5.—H. A. R—, æt. 20. A manic-depressive of some 4 years' duration who was first admitted in 1930 at the age of 16. During the succeeding 18 months he had several attacks of mania and melancholia, with practically no intervening period of normality. He recovered from this attack, and in February, 1932, was discharged after trial. Readmitted as a voluntary patient in January, 1934, he was very depressed, had lost all hope of getting well, and was preoccupied with ideas of bodily dysfunction. During his depressed phases he shows various schizoid traits, e.g., emotional blunting, seclusiveness, and autism, while in his manic phases he is exalted, argumentative, excitable, easily angered, mischievous and difficult to nurse. His family history is bad (parents alcoholic, three sisters and one brother patients here; two sisters and one brother manic-depressive and one sister schizophrenic. One brother outside spoken of as " peculiar "). Throughout the period of the tests he remained depressed, solitary, retarded, and voiced occasional mild somatic delusions.

| Date. | Blood bromine in mgrm. %. | Mental state at date of examination. |
|---|---|---|
| 30.i.34 | 0·46 | Depressed throughout whole period. |
| 6.ii.34 | 0·51 | |
| 16.ii.34 | 0·71 | |
| 23.ii.34 | 0·50 | |
| 22.iii.34 | 0·48 | |
| 28.iii.34 | 0·42 | |
| 4.iv.34 | 0·54 | |
| 13.iv.34 | 0·20 | |
| 20.iv.34 | 0·69 | |
| 28.iv.34 | 0·61 | |
| 15.v.34 | 1·01 | |

Average 0·55.

CASE 6.—H. G. W—, æt. 25. A case of dementia paranoides of some 3 years' standing, characterized by auditory hallucinations, delusions of persecution and of grandeur. His psychosis can be divided up into phases in which he is quiet, pleasant in manner, biddable and practically free from hallucinations, and phases during which he is very hallucinated, aggressive, hostile and resentful towards the staff, often to the point of attacking them.

| Date. | Blood bromine in mgrm. %. | Mental state at date of examination. |
|---|---|---|
| 23.iii.34 | 1·30 | Quiet phase. |
| 27.iii.34 | 0·88 | ,, ,, |
| 3.iv.34 | 2·35 | Excited and hostile. |
| 10.iv.34 | 0·68 | Quiet. |
| 14.iv.34 | 0·80 | ,, |
| 18.iv.34 | 1·84 | ,, |
| 25.iv.34 | 0·80 | Aggressive and hostile. |
| 1.v.34 | 1·14 | ,, ,, |

An analysis of these figures showed the factor of variability to be so great and so unrelated to particular clinical phases that it was felt that continuation of the experiments to assess variability would be unnecessary.

## THE PHYSIOLOGICAL BASIS FOR BLOOD BROMINE VARIATIONS.

A point of peculiar interest in the results here described is the wide variability in the values of blood bromine, not only from patient to patient, but also in the same patient after short intervals of time. Investigation has been made into

the nature of this variation. The possibility of a variable error in the method of investigation has been excluded as a result of large numbers of duplicate estimations.

### *Bromine Content of Food.*

A possibility to be considered is that variation might result from fluctuations in the bromine content of ingested foodstuffs. It has been shown that the blood bromine level, after the ingestion of large doses of bromide, is maintained at a value which depends upon the relative bromide intake, i.e., the relative proportions of bromide and chloride in the ingested foodstuffs (25); bromide excretion is facilitated by chloride medication, whilst on low chloride diets marked bromide retention occurs (26). Damiens and Blaignan (27) have shown that the relative bromide content of certain vegetable foodstuffs is subject to a ten-fold variation (the bromide contents varying from 0·17 mgrm. to 2·0 mgrm. per 100 grm. dry weight)—a point confirmed by analysis of various prepared foodstuffs in this hospital. Certain considerable individual differences are therefore to be expected as a result of dietary variations alone. Were this the sole cause, however, the daily variation of blood bromine in any one case would not be likely to exceed 0·1 mgrm.%. The results reported here show that figures exceeding this frequently occur. Accordingly it must be concluded that these variations are not the direct result of alterations in dietary bromide.

### *Effect of Chlorides.*

It is possible, however, that the bromine level in the blood is influenced by the amount of chloride taken in the diet, a low chloride diet resulting in accumulation of bromide in the blood, and vice versa (28). Kuranami (29) and Ewer (8) report that treatment with a single dose of sodium chloride results in a temporary fall in the blood bromine of rabbits, and our preliminary experiments with these animals indicated that this fall was sustained after continuous chloride medication. Extending the investigations, we chose five physically healthy schizophrenic patients, and fed them for 14 days on a diet containing on an average 2·8 grm. chloride per diem, making blood estimations at intervals of two days. Thereafter, for a period of 14 days, they were given salt solution to drink, resulting in a chloride intake of 15·9 grm. chloride per diem. In spite of this five-fold increase in chloride intake, with little variation in bromide intake (average values of bromide intake for the two periods being 3·9 and 4·1 mgrm. per day), no steady decrease in blood bromide was found, the average values of blood bromine remaining fairly constant, while individual values fluctuated widely. It appears, therefore, at least in the human subject, that variations in blood bromine are not wholly the result of dietary fluctuations, but are rather to be interpreted in terms of an internal redistribution of bromine between the blood and the tissues.

*Organism Tolerance and Bromide Storage.*

In cases in which the blood bromine is consistently low, the interpretation of this low value in terms of a diminished tolerance of the organism for bromide has to be considered. This interpretation is unlikely, however, since Quastel and Yates (30) have shown that after oral and intravenous administration of small doses of bromide in man, the rate at which bromide is removed from the blood is independent of the original resting value of the blood bromine. Bromide is stored in the tissues, but no particular organ appears to be able to concentrate large proportions of bromine and so act as a centre for redistribution. As a result, however, of simultaneous test-meal and blood bromine estimations, it was found, significantly enough, that the bromine content of the gastric juice increases abnormally when the bromine concentration of the blood is low, the inverse relationship indicating the possibility that a low blood bromine level may result from a hypersecretion of bromine into the gastric juice. It appears that alterations in bromine distribution between blood and tissues are similar in character to those observed with chlorides (31, 32) and water (33). If these are in any way controlled by the vegetative nervous system (cf. Kuranami, 1933) and changes in blood bromine are partly dependent on changes in affectivity, our work would show that this is most certainly not the only factor, and further, that such changes cannot at present be accurately evaluated.

## Summary and Conclusions.

(1) A study has been made of the blood bromine of 15 normal and 45 psychotic people over short periods.

(2) The blood bromine of normal males varies between 0·6 and 2·0 mgrm. %, while that of normal females showed wider variations at the lower levels, falling 0·25 mgrm. % in one instance.

(3) Of the male psychotics examined, low values were found indiscriminately in all types of schizophrenia, in paraphrenia, manic-depressive psychosis and involutional melancholia. One case of oligophrenia gave consistently low values. Psychoneurotics and organic dements gave values within the normal range.

(4) No correlation was observed between changes in mental state and variation in blood bromine.

(5) The estimation of blood bromine is of little value in the differential diagnosis of the manic-depressive psychosis.

(6) Individual blood bromine variations are endogenous in character, and are attributed to fluctuations in distribution of bromide between the blood and the tissues.

We wish to record our indebtedness to Dr. P. K. McCowan, Medical Superintendent of the Hospital, for his unfailing interest, advice and criticism during

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