XC. BLOOD-UREA CHANGES IN ABNORMAL MENTAL STATES AFTER THE ADMINISTRATION OF AMINO-ACID.

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(Received April 30th, 1932.)

A STUDY of the changes occurring in blood-amino-acid and urea following the ingestion of protein or glycine has been made, in order to determine whether any disturbance of nitrogen metabolism occurs in abnormal mental states. This work was suggested by a consideration of the disorders of carbohydrate metabolism found in psychotic subjects. There is general agreement that, while the fasting blood-sugar levels are within normal limits, in certain cases there is a lowered sugar tolerance and it has been recently established by McCowan and Quastel [1931] that a sustained hyperglycaemia is intimately associated with the affective state and varies *pari passu* with the degree of emotional tension experienced by the subject. It was thought possible that some comparable deviation from the normal might occur during protein breakdown and we therefore investigated the fasting blood in a series of cases and noted the changes in the amino-acid and urea levels at stated intervals following the administration of gelatin or glycine.

Our results, which are incorporated in the following paper, show that, among psychotics, the changes in the urea levels tend to be of a large order as compared with the normal and that two types of curves exist which are distinguished by variations in the rate of rise and fall of urea. Further, an association has been found between the type of curve and the clinical state.

Many investigations of the nitrogenous constituents of the blood in abnormal mental states have been made [Bowman, 1922; Henry and Mangam, 1925; Looney, 1924; Reid, 1927] but we have been unable to find any reference to changes occurring following protein intake. There is general agreement that in all forms of psychosis the urea-nitrogen lies within normal limits and Bowman in a survey of 229 cases found this to be true also of the other nitrogenous constituents. His findings were confirmed by Henry and Mangam. Rappleye [1919] noted low blood-urea levels among psychotics and Northcote [1932], working in this laboratory, found several low urea levels in an investigation of recently admitted cases of all types. She considered this to be largely due to an inadequate diet prior to admission. In our series, a generally low

fasting level has been found in the melancholic group and in four cases the value was below 20 mg./100 cc.

Folin and Berglund [1922] investigated the changes in the blood of a normal man following the ingestion of 25 g. of glycine and found that the amino-acid concentration reached a maximum in the 2nd hour and the urea showed fluctuations of a small order up to the 5th hour. They do not state under what conditions the subject was placed during the experiment. Witts [1929] studied the changes in amino-acid and urea following the administration of glycine in both health and disease and found that the amino-acid curve was remarkably constant, a peak being reached in about 2 hours, followed by a steady fall to normal. The maximum value for urea was reached in 2-4 hours after the peak of the amino-nitrogen curve. On giving 12.5 g. of glycine to a fasting normal subject he observed an increase of 2 mg./100 cc. in 3 hours followed by a steady fall to the fasting level within 6 hours.

Methods and procedure.

The subjects investigated, including controls, were between the ages of 17 and 55; all were in fair physical condition and in none was there any evidence of visceral disease. In the female cases the test was carried out during the inter-menstrual period.

The subject received no food after 6.30 p.m. on the day prior to the test, was in bed by 9 p.m. and remained there the following day throughout the period of the experiment. After a 14-hour fast a sample of blood was taken and a meal of protein or amino-acid administered. Venesection was performed at hourly intervals for 5 hours.

In the early cases gelatin was used, 25 g. being dissolved in 300 cc. of water and flavoured with 20 cc. of fresh lemon juice; this set as a fairly stiff jelly which was found to be generally unpalatable and difficult to administer. For this reason and because of its simpler constitution glycine was substituted in later experiments, 10 g. being dissolved in 100 cc. of distilled water and flavoured with lemon juice. Glycine was used in all the control experiments.

Estimations of amino-acids and urea were made by the Folin [1922] colorimetric and the Van Slyke and Cullen [1914] urease methods respectively, duplicate analyses being made in all cases.

RESULTS.

1. Amino-acid.

Amino-acid determinations were made on 17 consecutive cases of all types. The changes were small and varied but slightly from individual to individual. The total change was in no case greater than 3 mg./100 cc. and at the end of the 5-hour period the value had returned to within 10 % of the fasting level. The peak was reached generally in the 1st hour and never later than the 2nd, whilst the fall was gradual and uniform. The variations were so small

that no significance could be attached to the results and the determinations were discontinued in later experiments. No amino-acid estimations were carried out on controls.

2. *Blood-urea: results in controls.*

The subjects of the control experiments were four probationer nurses and a laboratory boy, all working at the Cardiff City Mental Hospital and examined under the same conditions as the patients. The blood-urea changes were of a small order, the maximum rise in no case exceeding 6.5 mg. per 100 cc. of blood (see Fig. 1), and in three cases being less than 1 mg. In every case

Fig. 1. Variations in blood-urea in a normal person after administration of 10 g. glycine.

there was evidence that the changes had reached their maximum before the end of the test period and a composite curve of this group as a whole is almost identical with that shown by Witts [1929], using the same quantity of glycine.

Results with patients.

Forty cases were examined and the results divide themselves into two distinct groups depending upon the rate of the changes in the urea levels. In both groups the changes tend to be of a large order.

Group 1 is characterised by a steady and uniform rise to a peak, occurring generally in the 3rd hour and followed by a rapid fall, the fasting level being reached in many cases by the 5th hour (*e.g.* Fig. 2). In addition the maximum changes, whether expressed in an absolute value of mg. of urea per 100 cc. of blood or as a percentage increase of the fasting level, were far in excess of the corresponding changes found in controls. The urea changes were about 14 mg. per 100 cc. of blood, or an increase of 50 % of the fasting level, a change which equals the changes found by Witts [1929] after the administration of double

the quantity of glycine to a normal subject. The variations between individuals were again marked but in only one case was the change less than 6.0 mg. per 100 cc. blood. The composite curve of this group shows none of the fluctuations commonly found both among normals and in Group 2.

Fig. 2. Changes in the blood-urea of a case of melancholia after administration of 10 g. of glycine.

Fig. 3. Blood-urea changes in a case of hebephrenia after the administration of 10 g. glycine.

Group 2 is distinguished both from the normal and from *Group 1* by the fact that at the 5th hour the value of the blood-urea is the highest observed during the test period, there being a relatively slow and gradual rise of the

urea level throughout the experimental period (*e.g.* Fig. 3). The successive changes up to the 5th hour were in no way regular and many cases yielded curves which exhibited a trough which varied in the time of its occurrence from individual to individual. The general extent of the final change is larger than normal but not so marked as in Group 1, and in many cases no differentiation based upon the actual changes could be made from the normal.

Melancholia.

Nineteen cases belonging to this group were investigated and it was found that all those in an acutely depressed or agitated condition belonged to Group 1 and gave the first type of curve (Fig. 2). The extent of the total changes appeared to be associated with the clinical state in that in the more agitated or depressed cases the urea level reached a higher peak and fell more rapidly than in the less severe cases. In three cases a high peak was reached as early as the 2nd hour and after a steady fall the urea showed a slight secondary rise in the last period. We repeated the test on one of these cases who had not changed clinically in the meantime after an interval of some weeks and found no change in the shape of the curve.

Six cases were found to give the second type of curve (Fig. 3) and were placed in Group 2; of these, three were showing good clinical improvement at the time of the test. They were in parole wards and interesting themselves in occupational therapy. Two others were retarded and listless and the last was in a good phase following continuous bath treatment.

A survey of the group as a whole leads to the conclusion that Fig. 2 is the characteristic finding in all agitated and acutely depressed cases while Fig. 3 occurs during improvement and in the less severe cases.

Relationship to emotional tension. The hyperglycaemic index, H.I. [McCowan and Quastel, 1931] is defined as "an expression of the sustainment of the hyperglycaemia found in many psychotic subjects" and its magnitude is a measure of the emotional tension of the patient, a finding corroborated by recent work on the galvanic skin reflex [Lockwood, 1932].

Taking the H.I. as the criterion we have found that the urea curve appears to offer no such objective standard of emotional tension; for although the H.I. was high in all the simple retarded cases giving the first type of curve, in two agitated cases presenting a curve of the same type it was zero. These findings suggest that Fig. 2 does not indicate the degree of emotional tension experienced by the subject.

Change of phase. In three cases, in whom no change in the physical or mental condition had been noted, the test was repeated after an interval of several weeks. The curve in each case presented no significant change. A fourth case was first investigated during a state of extreme agitation, when the curve obtained was of the first type showing a low fasting urea level with a marked and rapid rise and sharp fall to the fasting level. The test was repeated after

some months when he showed definite clinical improvement, the fasting urea level was now found to be normal and the curve approximated to that found in other cases showing improvement (Group 2).

Mania.

Two cases were investigated. They were examined in the acute stage within a week of admission and both were excited, restless, destructive and elated. In both these cases the fasting urea level was high and the curve showed little variation from the normal.

Table I.

		Mg. urea per 100 cc. blood								
		Hours								
		Age	Sex	Initial	1	2	3	4	5	Remarks
Melancholia	1. R.L.	28	F.	24.75	26.7	31	39.6	35	30	Agitated
	2. C.W.	43	M.	10.2	24.4	27	31.4	19.8	11.2	
	3. R.G.	35	F.	13.5	10.1	15.4	19.8	14	12.8	"
	4. N.L.	50	F.	31.5	32.5	41.5	39.7	—	36	"
	5. A.L.	38	F.	30.5	31.5	30	37.5	—	33	"
	6. L.T.	50	F.	14.5	24.6	35.7	27	24.3	26.5	"
	7. A.G.	53	F.	31.5	—	43.5	36	30	34	"
	8. L.B.	51	F.	31.5	31.5	29.5	34.5	39	37	"
	9. P.C.	53	F.	21	22.5	25.5	34.5	—	25.5	"
	10. J.E.	42	F.	33.9	31	39.6	31.8	33.4	36.4	Retarded
	11. B.A.	32	F.	24.8	27.8	39.3	41.4	25.5	21	"
	12. A.C.	32	F.	27	30	34	40	—	27	"
	13. B.J.	30	F.	27	30	28.5	34	—	30	"
	14. A.J.	32	F.	27.5	21.3	—	25.5	30	34	After continuous baths
	15. B.D.	30	F.	18	16.5	19.5	18	—	37	Very retarded
	16. T.M.	49	M.	26.8	18.6	29	25.8	30	37	"
	17. E.J.	22	F.	15.6	21.2	19.8	23.2	—	29.5	"
	18. E.M.	—	F.	30	33	39	36	39	45	Improving
	19. G.S.	—	F.	21	24	33	36	—	36	"
Mania	1. T.S.	43	M.	39	36	43	45	45	41	—
	2. H.G.	28	F.	40	41	43	43	45	41	—
Stupor	1. J.O.R.	38	M.	25.5	22.5	30	30	—	36	—
	2. G.G.	20	F.	25.5	22.5	24.5	24.5	—	84.9	—
Hebephrenia	1. D.L.	30	F.	27	30	30	33	—	33	—
	2. R.C.	32	F.	20	21.8	—	27	27	27	—
	3. G.W.	37	F.	35	31.8	31.8	39.4	36.8	42	—
	4. A.D.	28	F.	28	29	31.5	39	—	39	—
	5. R.N.	24	M.	25.5	19.5	21	21	21	31	—
	6. J.W.	33	M.	38	36.4	37	36.9	38	44.9	—
	7. H.C.	27	M.	27	27.5	30	30	34.5	41.8	—
	8. W.I.	20	M.	21	22.5	25.5	28.5	25.5	31.5	—
	9. D.J.	35	F.	29.2	31.7	36.3	40	—	37.9	Excited
	10. T.L.	21	M.	8.55	15	9	19.2	22.8	10.05	"
D. paranoides	11. J.B.	21	M.	42	36	36	41.5	42.5	45	—
	12. G.E.	33	M.	33	29.7	39	—	31.4	31.5	—
Catatonia	13. A.B.	21	M.	31	29.5	33	33	35.4	30	—
	14. G.N.	19	M.	23	26.5	27	30.6	27.8	28.5	—
	15. J.D.	38	M.	25.2	23.9	28.4	27	29	25.2	—
Mental defectives	1. N.R.	—	M.	28	21.5	31.5	28.5	35	36	—
	2. E.R.	—	F.	33	36	33	33	—	44	—

Stupor.

Two cases were investigated, one a catatonic stupor in a man aged 38 and the other a benign stupor occurring in a girl aged 20. In both the H.I. was zero. The results show both curves to be of the second type (Fig. 3), the initial changes fluctuating and of a small order and a sharp rise occurring at the 5th hour. Both these patients were fed on gelatin.

In the first of these cases the test was repeated after a month's interval; no change had been noted in the clinical state and the blood-urea curve showed no alteration.

Dementia praecox.

Fifteen cases were investigated, of whom eight emotionally flattened hebephrenics and one case of dementia paranoides gave curves of the second type (Fig. 3), while two hebephrenics, examined during a period of excitement, and one dementia paranoides conformed to the first type of curve (Fig. 2). In the remaining three cases, all catatonics, the curves approximated to the normal.

No definite conclusions can be drawn from these results but it appears that dull and apathetic states are associated with a relative delay in the rise of blood-urea.

In two mental defectives of unstable equilibrium the curves were of the second type.

DISCUSSION.

A consideration of the above results (given in detail in Table I) shows that a disordered nitrogen metabolism is associated with abnormal mental states, the disorder being most marked in melancholia where the blood-urea curve is of a particular type showing rapid and uniform changes of a large order. The urea level rises to a sharp peak and falls rapidly. This type of curve (Fig. 2) occurs in all acutely depressed cases whether of the agitated or simple retarded type, and was not found in the only two cases of manic excitement investigated. It cannot depend exclusively upon the degree of emotional tension present since it occurred in two cases in which the H.I. was zero. From the cases investigated during improvement and from the few cases on whom we were able to repeat the test it appears that, as the clinical condition improves, the rate of change in the urea level becomes less marked so that the curve undergoes a certain amount of flattening, the maximum reading being observed in the 5th hour. The actual changes still remained fairly large. This second type of curve (Fig. 3) is found also in states of stupor and in the majority of apathetic hebephrenics. The changes found in the dementia praecox group on the whole, however, show marked variations between individuals and we have been unable to attach any significance to our findings in this group.

The evidence is insufficient to form any conclusions as to the chemical nature of the changes we have described but they appear to be due, either to an increased urea formation or to a disturbance of those factors which control the rate of entry into and disappearance from the blood of urea. In view of the fact that no disturbance of urea formation has been observed even in gross pathological states of the liver [Mann, 1927; Van Slyke and Stadie, 1920; Witts, 1929] the former possibility appears remote. The various facts confirmatory of the close connection between mental disorder and endocrine dysfunction, coupled with

the observations of Addis, Barnett and Shevky [1918], who showed that adrenaline and pituitrin regulate urea excretion, make the latter suggestion more feasible.

SUMMARY.

1. The blood-amino-acid changes following the administration of gelatin or glycine to 17 psychotic subjects of varying types have been observed. There was no material difference from the normal among the different clinical groups.

2. The blood-urea changes following glycine or gelatin ingestion have been noted in 41 cases of psychosis and in 5 normal controls.

3. The normal blood-urea curve shows variations from individual to individual but the total changes are of a small order the maximum value being observed within 5 hours of the ingestion of the amino-acid.

4. The characteristic blood-urea curve of agitated and simple retarded melancholia is typified by rapid and uniform changes, the total extent of the changes showing a marked increase over the normal. There is a rapid rise to a high level followed by a rapid fall within the 5-hour period to the fasting level.

5. A second curve is described in which, while the early changes are fluctuating, the maximum reading is obtained later than in the normal the actual changes again being larger than the normal. This is found to occur during recovery from melancholia and in apathetic states generally. The rise in urea level is slow, reaching its peak at the 5th hour of the test period.

6. The clinical and biochemical aspects of these changes are briefly discussed.

We wish to express our thanks to Dr P. K. McCowan, Medical Superintendent of the Cardiff City Mental Hospital, and Dr J. H. Quastel (Director of Research) for their help and criticism during the course of this investigation, and to the medical officers for access to their cases. One of us (D. R. D.) is indebted to the Medical Research Council for a whole-time assistance grant.

REFERENCES.

- Addis, Barnett and Shevky (1918). *Amer. J. Physiol.* **46**, 39, 52.
Bowman (1922). *Amer. J. Psych.* **2**, 379.
Folin (1922). Laboratory manual of biological chemistry, 259.
— and Berglund (1922). *J. Biol. Chem.* **51**, 395.
Henry and Mangam (1925). *Arch. Neurol. and Psych.* **13**, 743.
Lockwood (1932). *J. Mental Sci.* (In the press.)
Looney (1924). *Amer. J. Psych.* **4**, 29.
Mann (1927). *Medicine*, **6**, 419.
McCowan and Quastel (1931). *J. Mental Sci.* **67**, 625.
Northcote (1932). *J. Mental Sci.* **68**, 263.
Rapleye (1919). *J. Nerv. Ment. Dis.* **49**, 130.
Reid (1927). *J. Mental Sci.* **63**, 254.
Van Slyke and Cullen (1914). *J. Biol. Chem.* **41**, 285.
— and Stadie (1920). *Arch. Int. Med.* **25**, 693.
Witts (1929). *Quart. J. Med.* **22**, 87, 477.