

THE BLOOD-UREA IN PSYCHOTICS.

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ALTHOUGH the blood-urea level is not uniformly distinctive of any type of psychosis or phase of a psychosis, yet its estimation in general psychiatric practice is probably as useful as any other test or reaction in use to-day.

The determination of the blood-urea by the urease method is simple to carry out, and with a good suction pump three sets of tubes can be aspirated simultaneously in series. Such a series can be prepared in half an hour, left with the pump on for an hour and a half, and finally disconnected and titrated in a further fifteen minutes—a total of three-quarters of an hour of actual laboratory work. This averages fifteen minutes for each estimation—no mean advantage in a busy hospital.

Walker (1, 2) and McCowan (3) have stated that nothing typical was found in a series of blood-urea estimations in psychotics, and that even in those with high blood-urea content renal disease was usually absent.

This paper, however, is not concerned particularly with the actual incidence of renal disease, but with the point of view that if a patient has a blood-urea of, say, 60 mgrm. %, then, notwithstanding the absence of renal disease, and whatever the type of psychosis, that patient has a definite abnormality which may be of clinical use as a guide to prognosis or treatment.

The blood-urea is subject to fairly wide variations in normal people, and de Wesselow (4) stresses the fact that urea is not a threshold substance but is purely a waste product; theoretically, it may fall almost to *nil*, and that although in most cases the diet is not of great importance, nevertheless a high protein diet may raise the normal level to 50 mgrm. %, or a very low protein diet reduce it to 12 mgrm. %. He also points out that adequate water must be available for the excretion of urea, and thus a high blood-urea may be due to the dehydration following an insufficient fluid intake.

Beaumont and Dodds (5) give the normal blood-urea level as 20–40 mgrm %. While pointing out the general reliability of this estimation, they mention that prolonged vomiting, intestinal obstruction and acute abdominal conditions increase the blood-urea, but such conditions are comparatively rare in a mental hospital, and could be ruled out in any individual case. They further state that the amount of nitrogen retention bears little relation to the extent of renal damage.

Shera (6), in an investigation of the urea content of the cerebro-spinal fluid and of the renal changes in 200 successive psychotics who were examined post-mortem, found abundant evidence of renal damage. He states that when the urea in the cerebro-spinal fluid is increased in the living subject the fluid is invariably under pressure and greatly increased in volume, and that in cases dying with high urea contents the brain shows obvious signs of recent compression and œdema, in marked contra-distinction to those yielding normal readings. He believes that this abnormal pressure had been operative as long as there had been nitrogen retention, and he brings forward evidence of pressure atrophy of cerebral convolutions resulting from it. In 78% of his subjects abnormal urea levels were found in the cerebro-spinal fluid, the reading being above 100 mgrm. % in 63%. Shera instances cases where the urea estimation was performed before and after death with no change in the result; but such extensive abnormalities are not so apparent in cases seen for the first time in the acute wards of a mental hospital as they are in subjects seen for the last time in a post-mortem room.

The statement advanced by Shera, that the urea content of the cerebro-spinal fluid is usually a measure of its pressure, does not call for separate estimations of the urea content of that fluid, since, as Greenfield (7) points out, the percentage of urea in the blood and cerebro-spinal fluid is almost identical.

The possible effect of toxic states on the blood-urea is illustrated by the observations of Shackle (8), who found greatly increased blood-urea levels in 27 of 35 patients twenty-four hours after ether anæsthesia. Seven of the remaining 8 cases had high blood-ureas initially. Age and duration of anæsthesia did not seem to affect the results.

The association of confused mental states with the toxicity of nephritic conditions is well recognized in almost every text-book of psychiatry, but one can agree with Shera that, in spite of their importance and frequency, renal lesions in psychotics do not receive the prominence and attention that they deserve.

It is obvious, of course, that any type of renal lesion might occur in a psychotic patient, and in particular the vascular types of nephritis, hyperpietic and senile or atheromatous, might be expected to be comparatively common. Such cases as the following are frequent enough:

CASE I.—Male, æt. 60.

History.—Gradual development of marked confusion with excessive restlessness and incoherence during the preceding twelve months.

Physical examination showed general flabbiness, the tongue was coated and tremulous, the teeth very carious. Heart-sounds clear, but arteries thickened and blood-pressure 190/120, pulse-rate 90 per minute. Pupils small and reactions sluggish, tendon reflexes exaggerated and inco-ordination of muscle movements present. The urine contained albumen and casts, and some pus-cells. The fluids were negative to tests for syphilis. Investigation showed the blood-urea to be 101 mgrm. %. This fell under treatment to 67 mgrm. % in one month, and improvement continued.

CASE 2.—Male, æt. 66.

History.—Gradual onset of dementia during the last seven years.

On examination he was confused and restless and complained of various persecutions, often attempting to beat off imaginary tormentors. The heart was enlarged and the blood-pressure high. The urine contained albumen. He had several uræmic fits following admission and died in one month. A week before his death the blood-urea was 190 mgrm. %.

Post-mortem examination confirmed the diagnosis of chronic nephritis and cardio-vascular degeneration.

Since tongue tremor, pupil irregularities and exaggerated tendon reflexes, with general flabbiness, are common in these cases, they may have to be differentiated from general paralysis, and occasionally even the examination of the fluid is not decisive, as the following case illustrates :

CASE 3.—Female, æt. 48.

History.—Two years before admission a change of character was noticed. She became unstable and worried about trifles, and suffered from periodic colds. Four months before admission she became depressed, and a month after this began to express grandiose delusions, which were prominent on admission, together with some confusion and restlessness.

Physically she was fat and showed a slight general icterus. The mouth was dirty and the tongue furred. The pupils were small and equal, and all reactions sluggish. Tendon reflexes exaggerated, blood-pressure 120/70, pulse-rate 65. The urine contained albumen. The cerebro-spinal fluid gave a positive Wassermann reaction, although the blood was negative. The Lange gold test read 233100000/05

Treatment was commenced with mercury and potassium iodide. The patient showed clinical improvement and the icterus faded, but following a seizure two months after admission, injections of N.A.B. were commenced. Further seizures occurred, and the blood-urea was found to be 91 mgrm. %. The fluids, on further examination, gave negative Wassermann reactions, and the patient later died in uræmic coma.

Post-mortem examination showed ulceration of the mouth and colon, while on microscopical examination fatty degeneration and cloudy swelling of the liver and subacute nephritis with superadded acute nephritis were found. There were no gross brain changes.

The difficulties of such a case as this are not so very exceptional. Moreover, uræmic states where the usual symptoms are lacking are well known and have been frequently alluded to in the past. MacAdam (9) in a recent communication again draws attention to latent uræmic states, where progressive languor, fatigue, loss of appetite and perhaps anæmia are present without albuminuria and probably without cardio-vascular changes, and the finding of a blood-urea between 100 and 200 mgrm. % proves the only means of establishing a diagnosis. Languor, fatigue, loss of appetite and anæmia are common enough in psychotic histories, frequently as precursors to confusional insanity, and the need for routine blood-urea estimations in such cases is apparent.

The recognition and treatment of even comparatively mild cases of renal damage is also very important sometimes, as is well shown by the following note :

CASE 4.—Female, æt. 52.

History.—This patient had been a worker in a mental ward of a Poor Law Hospital for six years, but progressive dementia had made her quite incapable of any voluntary effort, and she was certified.

On admission she was dull, lethargic and confused, almost stuporose.

A week after admission the blood-urea was 65 mgrm.%. The sole treatment adopted was the administration of a low protein diet. In fourteen days the blood-urea fell to 43 mgrm.%, and after a month it was 36 mgrm.%. She became a placid and useful worker, and is quite suitable for a parole ward.

Confusional Psychoses.

It will be apparent, from what has been said, that high blood-urea levels in psychotics are most commonly found in the confusional group.

In this investigation of 30 successive cases labelled “confusional insanity”, consisting of 11 males and 19 females, only 13 gave blood-urea findings that were always within normal limits. All patients were put on a fluid diet, and received a minimum of 80 oz. of fluid a day for at least three days before the blood-urea was estimated. Of the 17 cases with raised blood-urea levels, 6 gave figures between 45 and 70 mgrm.%, but none of these suffered from nephritis, although in each case the diet was arranged and graded to reduce the level to normal and to keep it so.

The remaining 11 cases, of whom 7 were males, suffered from chronic nephritis. Five of these had a blood-urea between 100 and 200 mgrm.%, and 6 between 60 and 100 mgrm.%, while confirmatory signs were found in all, both clinically and by laboratory tests. In no case did the treatment by diet and drugs fail to reduce the urea levels to within normal limits, but the ultimate result was generally not very satisfactory, since 6 of these 11 patients died, sometimes after striking clinical improvement followed by relapse, while only 5 of the 19 patients without nephritis died.

TABLE I.—*Confusional Psychoses.*

	Cases.	Deaths.
With normal blood-urea	13	} 5 (26%)
With raised blood-urea, but without nephritis	6	
With raised blood-urea and nephritis	11	6 (55%)

It would seem that in the presence of chronic nephritis the prognosis for a confusional insanity is distinctly worse, and the frequency of azotæmia in these cases demonstrates the importance of routine blood-urea estimations in such cases.

Mania.

Azotæmia is not confined to cases of confusional insanity. In 15 successive cases of mania 11 had normal blood-ureas. The average reading for this group of 11 was 27 mgrm.% soon after admission and after a month it was 33 mgrm.%.

some cases showing marked increases as from 22 mgrm. % to 44 mgrm. %, the result probably of insufficient food before admission and regular feeding afterwards. Age and blood-pressure did not seem to affect the results.

The remaining 4 cases had raised blood-urea levels, above 60 mgrm. %, soon after admission. One of these was a typical case of mania and had chronic nephritis, and the illness ran a course similar to any other case of mania.

The 3 others, without evidence of chronic nephritis, were all complicated by a degree of confusion, and they all improved very rapidly on a strict milk-and-water diet, and in one or two weeks were clear of all confusion, but still hypomaniacal. This state of hypomania continued for a few days or weeks before recovery, but the total duration of the illness was much shorter than is usual in ordinary maniacal attacks. One of these three was a certified patient for the fourth time, having had attacks of mania during two puerperal periods and also an attack of melancholia.

The clinical impression gained from these cases was strongly in favour of the diagnosis of a temporary toxæmia, including renal toxæmia, precipitating a psychosis in a manic personality. The recognition of the azotæmia and its treatment by a milk-and-water diet with fruit-juice and glucose did a great deal to hasten their recovery.

Acute Delirious Mania.

Blood-urea estimations in 3 cases of acute delirious mania suggested that these results were useful guides in prognosis. Originally the figures were high and remained so in the fatal cases, but fell to normal in one that recovered.

All 3 patients showed an acute restless delirium that was almost uncontrollable, 2 of them kept up a noisy and incessant flow of talk which showed well-marked flight of ideas (Cases 5 and 6), but the third, Case 7 in the table, was completely silent throughout and rather suggested a schizophrenic delirium in appearance. All were thin, bruised and seriously ill on admission and Case 7 had advanced pulmonary tuberculosis. The temperature of each ranged about 100° F., and the pulse-rate about 120 per minute. The mouth was foul and the tongue dry and coated, the bowels constipated and the sphincters uncontrolled. The pupils were extremely dilated and sluggish in their reactions; the knee and ankle-jerks were completely absent except in Case 7, where they were exaggerated. The blood-pressure was low, about 95/60, and the urine contained albumen and an abundant deposit of urates, with acetone in addition in Case 5.

Cases 6 and 7 died and Case 5 recovered.

The use of blood-urea estimations is obvious from this table (Table II), for it is useless giving protein foods until the blood-urea is falling. Every effort was made to give these patients sufficient fluid, so that the high figures were probably due to renal toxæmia and not to dehydration. Two deaths

in 3 cases may not seem to say much for the diet of 2 parts water to 1 of milk with glucose which was given to these cases, but the condition of the lungs found post-mortem in Case 7 made it a matter of wonder that she could have lived so long.

TABLE II.—*Blood-urea in Acute Delirious Mania.*

Days after admission.	Blood-urea in mgrm. %.		
	Case 5, æt. 19.	Case 6, æt. 24.	Case 7, æt. 30.
2	—	90	—
3	89	—	132
4	—	81	—
5	—	Died	—
6	—	—	121
9	—	—	Died
16	60	—	—
30	46	—	—

Melancholia.

High blood-urea levels were rare in 40 cases of melancholia and the level did not seem to be affected by the variety, whether simply depressive, acutely agitated or confused, nor by the blood-pressure, but there was a slight rise with advancing age, averaging 25 mgrm. % at 35 and 32 mgrm. % at 55.

Five patients had a blood-urea of 40 mgrm. % or a little over, which fell in one or two weeks to an average of 30 mgrm. %. One case only had a persistently high reading, varying between 50 and 90 mgrm. %. This patient steadily wasted and died. There was a history of attacks of jaundice and the passage of gall-stones, and advanced hepatic damage was found post-mortem. Two patients, with a history of refusal of food, had a blood-urea of less than 20 mgrm. %, and this rose to 33 and 39 mgrm. % respectively when tube-feeds were instituted.

Other Results.

In 9 cases of schizophrenia the blood-urea varied between 34 mgrm. % and 18 mgrm. %, with an average of 28 mgrm. %,—results appearing to be independent of the age and blood-pressure. Two further cases of schizophrenia gave abnormal results. In 1 a blood-urea of 53 mgrm. % fell to 18 mgrm. % in a fortnight—a case of azotæmia due to starvation. In the second case chronic nephritis and high blood-pressure were present, and the blood-urea was persistently in the neighbourhood of 40 mgrm. %.

In 11 cases of non-systematized delusional insanity the blood-urea varied between 21 mgrm. % and 48 mgrm. %, averaging 32 mgrm. %, and the higher readings were obtained in the older patients and in those (3) with raised blood-pressure.

In 9 senile cases the results varied from 25 mgrm. % to 50 mgrm. %,

averaging 37 mgrm. %. The blood-urea was rarely below 40 mgrm. % in those with high blood-pressure, even if albumen was regularly absent from the urine.

Normal readings were obtained in several cases of post-encephalitic psychosis and in mental defectives.

Puerperal Psychoses.

In 9 of 11 cases of puerperal psychosis the blood-urea was above normal soon after admission. Table III is an average table compiled from these cases :

TABLE III.—Average Puerperal Reading.

Day of puerperium . . .	14 .	16 .	18 .	20 .	22 .	24
Blood-urea in mgrm. % . .	51 .	46 .	44 .	38 .	35 .	23

The blood-urea normally falls before term and rises after labour. This rise is usually apparent between the tenth and twentieth days, the subsequent fall being independent of ordinary variations in diet, whereas in many cases of puerperal psychosis a satisfactory fall is dependent on a strict limitation of diet during the first few days in hospital.

The Blood-urea during the Malarial Treatment of General Paralysis.

The recognition, on purely clinical grounds, of the exact moment at which to terminate a course of malarial therapy is often difficult. To wait for such signs as persistent vomiting, collapse, cyanosis, seizures and jaundice is a dangerous procedure, and a convenient laboratory estimation of the degree of toxæmia or exhaustion would be of great service. Nicol (10) states that if more parasites than 35 are found in 25 fields on microscopic examination of a thin blood-film, then the infection should be stopped. The thickness of a thin blood-film is rather variable, however, and I have frequently seen counts much larger than 35 in 25 fields persisting for several days without danger. The blood-pressure falls during malarial therapy, but usually the fall is early and the level thereafter stationary, so that its measurement is not of any great use as an indication for the cessation of the pyrexia. In France the degree of azotæmia is often used as a measure of the toxæmia, and this is an excellent guide to the state of the patient's resistance to his infection in a majority of cases.

Both the blood-urea and the number of parasites per field tend to rise during the course of malaria, until a roughly stationary level is reached. This continues as long as the patient is holding his own with the infection, but once the malaria gains the ascendancy there is a progressive rise in the level of both; it is my experience, however, that the blood-urea level is the first to rise, and therefore is a more sensitive and reliable index.

Table IV is a typical picture of the changes in the blood-urea, the parasite count and the blood-pressure met with during treatment by malarial pyrexia.

TABLE IV.—Case 8, female, æt. 32.

Day.	Blood-urea in mgrm. %.	Malarial parasites in 25 fields.	Blood-pressures.		
			Systolic.	Diastolic.	Pulse-rate.
Before	39	—	122	88	85
1	46	0	—	—	—
5	—	20	90	45	95
7	49	37	—	—	—
9	—	61	90	60	80
11	—	60	—	—	—
12	52	61	90	60	70
14	59	44	80	50	72
15	71 (quinine)	77	85	55	75
18	47	—	—	—	—
22	37	—	90	50	80
24	29	—	115	80	75

In this table, the first day represents that on which the first rise of temperature to 102° F. or more occurred. The patient was seriously ill on the 15th day when quinine was given.

The following table shows the findings in two cases of general paralysis where death occurred, in the first from malaria, after quinine, even in the largest doses, had failed to stop the infection and daily rigors continued unabated, and in the second from progressive toxæmia following the cessation of malaria.

TABLE V.

Day.	Case 9.		Case 10.	
	Blood-urea in mgrm. %.	Malarial parasites in 25 fields.	Blood-urea. in mgrm. %.	Malarial parasites in 25 fields.
Before	38	—	38	—
2	36	4	49	0
7	76	15	43	27
8	59	30	—	13
9	78	24	70 (quinine)	29
10	81 (quinine)	28	—	—
11	91	56	—	—
13	Died	—	—	—
14	—	—	99	—
16	—	—	122	—
18	—	—	177	—
21	—	—	Died.	—

In this table also, the first day is taken as that on which the temperature first exceeded 102° F.

As a rule the blood-urea should not exceed 70 mgrm. % during malarial therapy, for increasing toxæmia may kill the patient despite the administration of quinine if this level is exceeded. When the blood-urea is more than 45 mgrm. % it should be estimated daily, for the rise is often rapid and a day missed may be of vital importance.

No outstanding results were found in cerebral syphilis, or during treatment with N.A.B. or other anti-syphilitic drugs.

The Blood-urea during Non-specific Protein Therapy.

It is well known that during the pyrexia of non-specific protein therapy there is a degree of nitrogen retention in the blood. This azotæmia is usually more marked in confused patients who are obviously physically ill. I have not met with any very high blood-urea levels during treatment with T.A.B. vaccine, chiefly because severe reactions are avoided, in the belief that the dangers of sudden heart failure and of hepatic or renal damage are very real, and that results are equally satisfactory with a series of maximum temperatures of 102° F. or even less; but I consider that where hepatic or renal insufficiency is suspected the blood-urea should be estimated before injection and at six hours and twenty-four hours after, a high and prolonged urea retention being a danger-signal.

The following table compares the findings in a healthy schizophrenic, æt. 23, and a confused alcoholic, æt. 34. The maximum temperature in each was 102° F.

The blood-pressures are shown, and although there is an initial rise of systolic pressure followed by a fall, the diastolic pressure falls almost uniformly, and the blood-urea is roughly inversely proportional to it.

TABLE VI.—Case 11: *Schizophrenic female, æt. 23.* Case 12: *Alcoholic Confusion, female, æt. 34.*

Time.	Case 11.			Case 12.		
	Blood-urea in mgrm. %.	Blood-pressure.		Blood-urea in mgrm. %.	Blood-pressure.	
		Systolic.	Diastolic.		Systolic.	Diastolic.
Before injection .	28	120	80	28	90	60
2 hours after injection	28	130	78	35	95	55
4 " "	36	140	70	41	85	55
6 " "	34	108	60	45	70	40
8 " "	39	98	52	40	80	45
10 " "	33	110	60	46	75	45
24 " "	22	120	85	39	85	55

The possible uses of blood-urea estimations during treatment with T.A.B. vaccine are fairly evident from this table.

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