INVESTIGATION OF THE ACID-BASE BALANCE IN MENTAL CASES, WITH SPECIAL REFERENCE TO EPILEPSY.

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HISTORICAL.

IN the search for somatic disturbance in connection with the insane, either as a cause or as an effect of mental disorder, the acid-base balance has afforded a field of exploration from time to time. Epilepsy, in particular, has provided material for research on these lines. Bigwood (1) (1924) suggested that the epileptic seizure was preceded by an alkalosis, leading to a lowered blood-calcium content, which, in turn, induced the fit. Marrack and Thacker (2 and 3) (1926) disproved this theory, but found that a high blood-ammonia content obtained at times in epilepsy (4), but was not related to the fit. It was actually a starvation phenomenon. There has been biochemical work on other lines in epilepsy in regard to nitrogen retention (5) on the sugar content, but all with negative results.

More fruitful results have recently (1927) followed the work of Robinson, Russell Brain and Kay (6) on the blood-cholesterol in epilepsy. A definite fall of cholesterol is registered prior to the fit, with a subsequent return to normal.

Notwithstanding the hitherto negative character of the results of acid-base studies in epilepsy, it was thought worth while to investigate a number of cases of unclassified new admissions to Hellingly in respect of their acid-base equilibrium and also to compare them with epileptics, and to investigate the reaction of the blood, particularly the alkali reserve, in relation to the fit.

Actually, some valuable information has been obtained in the course of this investigation, which also throws light upon the value of institutional treatment in the early stages of mental disorder.

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Technique.

It should be stated at the outset that the reaction of the blood as stated in terms of hydrogen ion concentration affords less information than the more searching assessment of the alkali reserve. It is, however, of confirmatory value, and the technique is described as affording a satisfactory alternative to the more expensive hydrogen electrode method.

Austin-Cullen Method of Estimating the Hydrogen-ion Content of the Plasma.

Standards.—The bicolour principle is used—that is to say, the acid and alkaline tubes are made up with phenol red separately and superimposed in the comparator. Buffer standards are unnecessary in this method and the colours are fast. Stability and freedom from temperature effects are additional advantages of the bicolour principle. The standards can be made in any laboratory and are invaluable for media work. However, exactly similar tubes in regard to thickness and diameter are essential. A gauge should be used (supplied by Baird and Tatlock) for testing the diameter.

The standards are prepared as follows:

Required: Phenol red, 0·1% (stock solution); N/100 NaOH (freshly made); N/10,000 HCl; one microburette; test-tubes of exactly similar diameter and thickness; a three-row wooden comparator block of at least 6 tubes.

Procedure: 15 c.c. of 0·1% phenol red are diluted to 200 c.c., yielding a 0·0075% solution. In each pair of standard tubes the total amount of indicator = 2·5 c.c. The total volume of the solution in each tube = 25 c.c.

The table herewith given shows the amounts of 0·0075% indicator solution to be added, also the amounts of acid and alkali respectively for the appropriate pH values:

pH at 38° C.	Alkaline tube.		Acid tube.	
	c.c. of dye.	c.c. of alkali.	c.c. of dye.	c.c. of alkali.
7·0	0·46	24·54	2·04	22·96
7·05	0·50	24·50	2·00	23·00
7·1	0·55	24·45	1·95	23·05
7·15	0·60	24·40	1·90	23·10
7·2	0·65	24·35	1·85	23·15
7·25	0·71	24·29	1·79	23·21
7·3	0·77	24·23	1·73	23·27
7·35	0·84	24·16	1·66	23·34
7·4	0·90	24·10	1·60	23·4
7·45	0·97	24·03	1·53	23·47
7·5	1·04	23·96	1·46	23·54
7·55	1·11	23·89	1·39	23·61
7·6	1·18	23·82	1·32	23·68

The tubes must be sealed. A well-fitting cork and a thick covering of collodion suffices.

Determination of the pH of serum or plasma.—The blood is collected from a vein without stasis. To this end, when the needle is in the vein the tourniquet is relaxed and the arm raised vertically and held there for thirty seconds, keeping the needle in position. It is then lowered, and with hardly any suction blood is aspirated to the extent of 8 c.c. A paraffined centrifuge tube is then taken and the blood runs down beneath liquid paraffin as illustrated on p. 456.

The paraffin rises above the blood and so contact with air is avoided. A few crystals of oxalate have been previously placed at the bottom of the tube, and when the blood is delivered it is mixed by placing the thumb on the end of the tube (A), drawing it up nearly to the surface and then releasing the thumb. This is done repeatedly.

The blood is next spun until clear plasma is seen.

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Adjusted saline solution is prepared thus: 0·9 grm. sod. chloride is dissovled in boiled neutral (pH 7·0) distilled water in 100 c.c. flask, then 10·5 c.c. of ·0075% phenol red solution (see above) are added. The mixture is made up to 100 c.c.

Control solution: A similar solution of salt without phenol red is made.

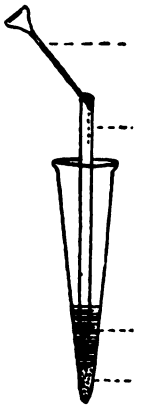
The adjustment: At the beginning of each experiment, after addition of phenol red the solution is covered with liquid paraffin. 1/100 N. NaOH is admitted by capillary pipette until a pH of 7·4 is reached, which is the normal blood pH.

The actual test of the plasma pH: No. 1 tube.—4 c.c of adjusted saline indicator are pipetted under paraffin into a small test-tube (1·5 × 10 cm.). After the addition of 0·2 c.c. of plasma the mixture is gently stirred with a footed glass rod.

No. 2 tube.—A control tube is used in a similar manner, using saline solution *without* the dye.

The liquid paraffin is replaced by melted hard paraffin, which is allowed to solidify. This prevents change of pH due to absorption of aerial CO_2.

A thermometer is inserted in the control tube, and both are brought to a temperature of 39° C. by immersion in water, which is gradually warmed up. When the temperature reaches 38° they are quickly arranged in the comparator block and matched off. Some considerable practice is required for accurate matching.



Estimation of the alkali reserve.—The method used was Van Slyke's plasma bicarbonate method. Plasma was used throughout, and care was taken that the syringe used for collection was carefully rinsed with strictly neutral saline. Venous stasis was avoided as above indicated. Normal ranges are 52–79 vols. CO_2%, with an average of 65·5 vols. CO_2%.

Sellard's acidosis test: Neutral absolute alcohol is required; also 0·5% phenolphthalein. One c.c. of serum is mixed with 25 c.c. neutral absolute alcohol. A precipitate of proteins occurs and is removed. The filtrate is evaporated after adding phenolphthalein to the extent of a few drops.

Normal sera turn pink on evaporation. In slight acidosis the pink colour is deferred; in severe acidosis it fails to appear. The test is held to be clinically reliable.

The acidosis ratio of the urine: the ratio $\frac{\text{urea nitrogen}}{\text{ammonia nitrogen}}$ is worked out. The urea is measured by one of the hypobromite methods (we use that of Doremus) and the ammonia by the formalin method. The molecular weight of ammonia being 17, the nitrogen fraction of ammonia is $\frac{14}{17} = ·0056\%$. The nitrogen fraction of urea is $\frac{7}{15}, = ·466\%$. The normal ratio $= \frac{\text{urea nitrogen}}{\text{ammonia nitrogen}} = 20:1$. A ratio of 10 : 1 or less indicates acidosis.

Indican estimation.—The urine is extracted with chloroform and then shaken with Obermeyer's reagent (0·2% ferric chloride in conc. HCl): Chloroform 3 c.c., urine 5 c.c., reagent 5 c.c. Shake for one minute and stand.

Excess of indican (normally absent) is shown by the development of a Prussian blue colour in the layer of chloroform.

Results.

All experiments were performed twice on the same specimen, and any inconsistent results were discarded. Seven volunteers, including the laboratory staff, supplied normal controls. The results are summarized as follows:

—	Normals.		New admissions (unclassified).		Chronic cases (unclassified).		Epileptics.	
	Number tested.	Average reading.	Number tested.	Average reading.	Number tested.	Average reading.	Number tested.	Average reading.
Venous plasma pH	7	7·364	28	7·314	30	7·326	47	7·348
Alkali reserve	7	68·83	25	57·73	31	56·65	48	66·009

Estimated by the Van Slyke method as volumes of CO_2 capacity *per cent.*

Epilepsy.—It will thus be seen that, as compared with the normal subject, the new admissions and chronic cases show *a distinct average tendency to acidosis*, whereas the epileptics deviate but little from the normal.

This points to epilepsy as a disorder in which the disturbance of nutrition and metabolism generally is decidedly *less* than that of the average mental patient who definitely shows signs of mild acidosis. A number of further observations were conducted in addition to the above in respect of the variation of the alkali reserve (a much more delicate indicator than the plasma pH) in epilepsy in relation to (*a*) meals, (*b*) fits, (*c*) *status epilepticus*.

(a) *In relation to meals*, five three-hourly curves worked out. No pathological variations occurred. These included two cases of epilepsy, two of dementia præcox, and one of general paralysis.

(b) *In relation to fits*, the following data are significant:

Case	Date of nearest fit.	Date of test.	No. in preceding four weeks.	V.S.	pH.
H—	Oct. 4, 1927	Oct. 3, 1927	1	59·39	7·35
H—	Oct. 5, 1927	Oct. 4, 1927	9	75·19	7·325
S—	Oct. 6, 1927	Oct. 7, 1927	9	74·2	7·35
B—	Oct. 9, 1927	Oct. 10, 1927	3	83·4	7·325
B—	Oct. 15, 1927	Oct. 14, 1927	2	82·3	7·325
T—	Oct. 20, 1927	Oct. 21, 1927	10	65·2	7·325
E—	Oct. 27, 1927	Oct. 27, 1927	10	53·5	7·35
D—	Dec. 12, 1927	Dec. 12, 1927	7	70·7	7·35
D—	Dec. 14, 1927	Dec. 14, 1927	7	70·0	7·35
D—	Dec. 15, 1927	Dec. 15, 1927	7	67·1	7·35

It is thus obvious that far from there being any question of acidosis before or after the fit, the alkali reserve and pH are well up to normal. There is in the majority a tendency to alkalosis.

(c) *Status epilepticus.*—A specimen taken during *status epilepticus* whilst the patient was still dazed showed a reading of 67·2 vols. CO_2 capacity *per cent.* In view of previous results this is not surprising.

We are thus brought to the conclusion that there is no marked deviation from the normal alkali reserve in epilepsy, which is a remarkable tribute to bodily powers of adjustment under severe stress, and confirms the findings of Marrack, Thacker and Lennox.

Acidosis in new admissions.—The question of acidosis in new admissions has been investigated *viâ* the blood, and as we have seen, the average tendency of the alkali reserve is towards the low side. The problem was likewise approached from another angle—that is, from the urine. One fallacy had to be guarded against, namely renal disease, both in respect of acidosis and in respect of a parallel investigation in regard to protein intake.

A series of 34 cases showed: Low protein intake (urea less than 1·5%; normal 2% or over), 15 cases, = 44·1%. Renal disease as evidenced by albumen and casts, 3 cases = 8·8%. Indican (intestinal toxæmia), 19 cases, = 52·9%.

The high percentage of cases showing low protein intake and intestinal toxæmia is very significant. It confirms clinical observation as to the evils arising from semi-starvation and constipation, both so common in the untreated mentally diseased.

There is little doubt that the improvement in mental condition a few weeks or months after admission is due in no slight degree to the way these two factors are influenced by proper mental nursing, and affords statistical evidence of the necessity for such nursing.

These 34 cases showed: Abnormal acidosis ratio in 4 cases = 11·7% (9 : 1, 6·65 : 1, 9·6 : 1, 9·02 : 1). Ketosis in 6 cases, = 17·6%. Sellard's acidosis test was positive in 2 cases, = 4·8%.

Hence this series show a small but definite percentage of relatively severe acidosis apart from the general average of mild acidosis.

At Cardiff Dr. Goodall found a heavier incidence of severe acidosis in new admissions. Only 4 out of 32 cases showed a Van Slyke of over 53 vols. CO_2 and 28 ranged from 53–42 vols. It must be remembered, however, that malnutrition is more common in the urban population whence these latter results accrue than in such a district as East Sussex, which is mainly agricultural.

What it comes to is this—that in new admissions previous malnutrition as a result of difficulty in feeding may have led to starvation acidosis. On the other hand, this will not explain

why the chronic case should show a tendency to acidosis. There seem to me to be several possible explanations. One is that some depletion of the alkali reserve is an accompaniment of chronic mental disorder with the exception of epilepsy, possibly as a result of toxæmia (dental or alimentary), or as a result of disordered endocrine metabolism. At any rate, this alteration affords one more instance of faulty metabolism, and in order to guard the patient from further somatic damage the building up of the alkali reserve should, where indicated, be undertaken by means of alkaline treatment. The procedure followed at Cardiff, whereby all new admissions are investigated in this connection, seems entirely admirable. Doubtless it is being followed up in a therapeutic manner.

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