STUDIES FROM THE PATHOLOGICAL LABORATORY, BETHLEM ROYAL HOSPITAL.

BRIEF EXPLANATORY NOTE.

BY J. G. PORTER PHILLIPS, LONDON.

FOR the benefit of some readers it has been thought advisable to preface the following researches by an explanatory note.

In the first instance the investigators engaged were prompted to prosecute inquiries into certain physiological phenomena occurring in varied mental states, by the fact that certain modification and amelioration of signs and symptoms were noticed to occur when treatment of an empirical nature was employed. These clinical observations have been made by me and others over a period of many years, and their real nature demanded a scientific explanation.

It is pleasing to note that each of the three investigations entered upon has been approached with a totally unbiased mind, and without any object in view of satisfying the demands of either the psychical or physiological school, as to the genesis of the various mental states dealt with.

The results are intended to record exact findings—as facts to correlate with others—with the hope that sooner or later certain definite postulates can be laid down and concepts formed as to the pathological mechanisms entailed.

I.—THE PHYSICAL FACTOR IN MENTAL DISORDERS.

BY H. S. LE MARQUAND, LONDON.

Just as the development of a bacterial infection depends on the relation between the virulence of the invading organism and the resistance of the host, so, many forms of mental disorder appear to depend on the relation between the severity of the psychic disturbance and the mental stability of the patient. The following article is the account of an investigation of a number of patients, with a view to the discovery of some fresh factor in the production of the psychoses. The amount of complement in the blood, the

degree of alkalinity, and the surface-tension of the serum were determined in each case.

The Complement in the Psychoses.—The patients can be roughly placed in the following classes of insanity:—

	Cases.			Cases.
Manic-depressive psychosis ..	6	Dementia præcox	19	
Dementia paranoides and para-		Psychoneurosis	8	
phrenia	14	General paralysis	5	
Melancholia	18	Various	20	
Confusional insanity	7			
Paranoia	3	Total	114	
Dementia	4			
Mania	10			

The amount of complement was determined in the following way. The blood of the patient, obtained from the median basilic vein, was centrifuged, and the serum diluted to 1 part in 10 with 0·9 per cent NaCl. In each case a hæmolytic system was put up with six different dilutions of serum. The tube with the highest dilution of serum contained 1·5 per cent of serum or 3 parts of the 1–10 solution, and the tubes varied by 0·5 per cent up to 4 per cent of serum in the tube with the lowest dilution. The same amount of sensitized blood-corpuscles (5 per cent suspension) was added to each tube, and the volume equalized with 0·9 per cent NaCl. Thus the sensitized blood-corpuscles consisted of 0·5 per cent of hæmolytic serum of a titre of 1–3000 in 5 per cent suspension of sheep's red cells in normal saline. After an hour in a water-bath at 37° C., the degree of hæmolysis was noted, that is, the amount of complement was determined. The tubes were classified under the headings 'no hæmolysis', 'slight hæmolysis', 'extensive hæmolysis', and 'complete hæmolysis'. No tube was counted under the last heading if a trace of red corpuscles remained unhæmolyzed.

The quantity of complement in normal blood was estimated in 1909 by MM. Jacobæus and Bachman.¹ Using the same method, they found that complete hæmolysis was obtained in the great majority of normal people with dilutions of serum representing 0·8 to 2 per cent. Our series of normals was taken from the nurses and attendants of the hospital, and we did not obtain hæmolysis in such low dilutions. In a few cases hæmolysis was complete with 1·5 per cent of serum, but the majority did not hæmolyze completely with 2 per cent of serum. Compared with the results of M. Jacobæus the amount of complement appeared low.

We found that the amount of complement in the 114 cases of mental disease varied very considerably, but practically within the limits of normality. On examining the results of each of the above groups there is found no very marked difference between them,

except that the dementia paranoides and paraphrenia cases show a rather high amount of complement. In the group of 18 melancholics there is a great variation, some hæmolyzing in very high dilutions, others scarcely at all in low dilutions.

To determine whether the complement varied with the physical or mental condition of the patient, and to ascertain if it were a constant factor for each individual, a number of these patients were examined on two or more occasions. Of 33 cases examined more than once, 13 were in very much the same condition both mentally and physically on each occasion. Of these 13, 9 showed the same or almost the same degree of hæmolysis, 3 showed less, and 1 rather more extensive hæmolysis on the second occasion. In only 2 of the 4 cases which did change was the change pronounced. In 20 cases there was a considerable change in the mental and physical states. Of these, 6 showed the same degree of hæmolysis, in 5 there was more extensive hæmolysis, and in 9 the hæmolysis was less pronounced. Therefore it may be deduced that for a given individual the complement tends to remain constant in quantity, unless there takes place a very pronounced change in his condition.

Analyzing these cases still further, we find that in 6 of them marked physical and mental deterioration had taken place. Of these cases, 1 remained the same, 2 hæmolyzed more, and 3 less than before. In 8 cases mental and physical improvement had taken place; of these, 4 remained the same, 3 hæmolyzed less, and 1 more than before. A deterioration, then, leads to a more marked change in the complement than an improvement in condition.

But though the change in the amount of complement is apparently altered by the physical and mental changes of the patient, yet the absolute amount of the complement does not depend on the physical condition. For example, in 17 cases of the series picked out for their bad physical condition (and bad mental cases also, as it happens), in 9 the complement was on the high side, in 5 on the low. Or, if we take the cases with a low hæmolysis, we find that of 22, 15 were in good, 4 in poor, and 3 in fair physical condition; while of 47 cases with a high hæmolysis, 32 were in good, 8 in poor, and 7 in fair condition.

In some cases of marked physical wasting, the complement remained high all through. It may be mentioned that in one case of general paralysis the amount of complement was largely increased during a seizure.

REFERENCE.

- ¹ BACHMAN, LOUIS, and JACOBÆUS, H. C., "Sur la quantité de complément et d'ambocepteur, et la quantité hæmolytique du sérum humain physiologique", *Comptes rend. Soc. de Biol.*, 1909, lxxvii.

II.—THE ACID-BASE EQUILIBRIUM IN CASES OF MENTAL DISORDER.

BY C. J. THOMAS, LONDON.

The object of the following part of the investigations was to discover what pathological basis, if any, could be found to account for the bodily and mental improvement of some cases of mental disorder under alkaline therapy recorded by various clinicians.

J. J. M. Shaw¹ considers a 'hypo-alkaline state of the blood', due to the production of acid substances from excessive nucleoprotein breakdown, as a contributing factor in the causation of the convulsive seizures of epilepsy, and reports several cases greatly improved by the administration of alkalis, though he claims only temporary amelioration.

Guidi² concluded, from estimations of the ammonia excretion of the urine of epileptic patients, that acid intoxication was an important feature of epilepsy, as the amount of ammonia excreted is greatly increased before a fit. He assumes that the amount of ammonia eliminated corresponds to the degree of acid intoxication.

B. H. Shaw³ states that many fresh admissions are in a state of acidosis, especially in cases of acute delirium, melancholia, confusional and stuporose states, and epilepsy. He also considers that acidosis may be a factor in the production of epileptic fits. His views are based among other points on the discovery in these cases of acetone bodies in the urine, and on the time incidence of epileptic fits varying with the diurnal changes in the hydrogen-ion concentration of the blood. He gives examples of cases which improved under alkaline therapy, and states that in cases which recovered it was noteworthy that the improvement synchronized with diminished acidosis.

Walker,⁴ in his observations on the urea concentration in the psychoses, notes that all the cases of dementia præcox in his series showed a moderate to a marked degree of acidosis, the statement being based on the ammonia excretion of the urine. Acidosis was not found by him in mania, melancholia, or insanity with epilepsy, but to a mild degree in eight cases of confusional states. A severe acidosis was also recorded in his only case of general paralysis. If there is an acidosis present, as some of these observers believe, we have at once a pathological condition present pre-eminently responding, for the time being at any rate, to alkalis.

The acidosis need not necessarily be a ketosis, though even here we were unable to confirm the frequent acetonuria met with by Shaw in admission cases. The degree of acidosis in any particular case may be estimated in several distinct ways. Clinically the measurement of the actual hydrogen-ion concentration of the blood is useless, the

neutrality of the blood being so elaborately guarded, as any considerable increase of hydrogen concentration is incompatible with life. Estimation of the alveolar CO_2 (which gives us a measure of the available sodium bicarbonate) in mental subjects presents difficulties so insuperable that this method of investigation was discarded. Van Slyke's definition of acidosis as "a condition in which the concentration of bicarbonate in the blood is reduced below the normal level", although not universally applicable, is of great practical importance. The deficiency of bicarbonate gives a measure of the ability of the blood plasma to hold the hydrogen-ion concentration of the blood constant when foreign acids are being introduced. We therefore took the blood specimens of 100 to 120 cases at random, but excluding cases of insanity with epilepsy (which we are investigating separately), and determined the CO_2 combining power by van Slyke's method. The whole blood was used in each case, and was brought into equilibrium with alveolar air for the experiment. A drop of secondary octyl alcohol was introduced into the apparatus for each experiment, to prevent frothing of the blood. The CO_2 combining power varies considerably, but in normal people has been found to be constant within the limits 55 to 75 per cent. The average of our series was 62.27, which would appear to be well within the normal limits decided by other workers.

The four cases which were below the level of 55 per cent were not considerably below, the lowest being 47 per cent. One of these cases was dementia præcox, two were toxic confusional states (puerperal), and the remaining one was a senile melancholic, very resistive and spoon-fed. The general appearance of these patients was suggestive of a severe toxæmia. All were sallow and unhealthy in complexion, one having marked pyorrhœa. It is interesting to note that the van Slyke readings of one puerperal case, taken at different times in the course of her progress towards recovery, were 48.39, 52.98, 58.45, 66.98. This patient on admission was childish and fatuous, but steadily improved until she was discharged quite recovered. With the increase in the bicarbonate figure her toxic appearance gradually disappeared. At no time during her illness could acetonuria be detected.

An analysis of 18 cases with alkali reserves which, although not abnormal, were less than 60, showed :—

Cases				Cases			
Dementia præcox	..	..	} 6	Melancholia	..	..	3
Dementia paranoides	..	..		Manic-depressive insanity	..	..	2
G.P.I. (advanced)	..	..	2	Hysteria	..	..	1
Toxic confusional—				Paranoia	..	..	1
Alcohol and drugs	..	..	1	Confusional, with gross cardiac			
Puerperal	..	..	1	disease	..	..	1

The hæmatocritic indices of the blood of these cases were determined and found to be normal. The second method of investigation employed was 'the alkali tolerance test' (Sellards). Briefly put, it consists in ascertaining the amount of sodium bicarbonate that must be taken by the mouth in order to make the urine alkaline. In a normal person 5 gm. will usually effect this alteration, 10 gm. being the outside limit for a man. Sellards states that a deficit of 20 gm. of sodium bicarbonate produces a degree of acidosis only demonstrable by examination of the blood.

The actual procedure was as follows: The hydrogen-ion concentration of a specimen of urine passed before the commencement of the experiment was first estimated colorimetrically. To 5 c.c. of the filtered urine was added a definite quantity of an appropriate indicator. The p_H of the urine being usually between 5 and 6, methyl-red or brom-cresol-purple was commonly used. A series of solutions of known p_H were accurately prepared according to the tables given by Cole; 5 c.c. of each solution of known p_H were placed in similar tubes to the urine, and the same amount of indicator added to each. The tints were now compared in a comparator, and the p_H of the urine was thus ascertained. The patient's bladder was emptied and sodium bicarbonate given in 2-grm. doses in a definite quantity of water. At the expiration of each half-hour the p_H of the urine was determined, until at last the p_H of the urine was the same as that of the blood, i.e. 7.4, using brom-thymol-blue, phenol-red, or cresol-red as indicator in the latter stages. If the urine was obviously keeping acid, larger quantities than 2 gm. were administered at a time. The patient's weight was also taken, as the amount of bicarbonate required varies proportionately with the weight of the body fluids. The majority of patients responded to this test as normal individuals. Too frequently to be a coincidence, it was observed that the alkali tolerance of tube-fed patients was increased. In our series, one patient with nephritis, whose alkali reserve was 65.7, had a markedly increased alkali tolerance, while the urine in the confusional case (with heart disease) was decidedly acid after the administration of 14 gm. With the exception of these cases of gross bodily disease, we found it not uncommon to detect deficiencies of 14 or 16 gm., while even 18 and 20 gm. were recorded. A typical uncomplicated case gave results as follows:—

Before experiment	..	2	4	6	8	10	gram. NaHCO
p_H urine	..	5.0	5.8	6.8	7.3	7.7	7.9

showing 6 gm. to be the approximate alkali tolerance.

The most marked increases in the alkali tolerance were found in cases of dementia præcox and in toxic confusional states (especially puerperal cases). Thus a young girl with dementia præcox, weighing

just 70 lb., needed 16 grm. to make the p_H of her urine 7·5, while in another case the administration of 16 grm. only caused the p_H of the urine to rise to 7·05. A puerperal case with an alkali reserve of 52·9 required 14 grm., and a toxic-looking stuporose case required 16 grm. Of the first 50 cases we examined, 8 had a tolerance above 14 grm., 3 of which were due to obvious bodily disease, 3 were toxic confusional states, and 2 dementia præcox. A slight increase in bicarbonate tolerance (10 to 14 grm. required) was found in 7 depressed cases.

Our results show therefore that in the great majority of cases of mental disorder there is no acidosis whatever, but that a small group exists in which a slight degree of acidosis can be detected. This group responds very well to alkaline therapy, the dosage of which can be regulated easily by simple tests on the urine. In a few cases the immediate response to alkalis is very striking, but is not sustained. This is usually due to the coincident toxæmia, appropriate treatment for which should be used energetically. Thus, in a case of puerperal insanity, treated in consultation with Dr. S. R. Tattersall, immediate bodily and mental improvement was noticed, the excited, incoherent state on admission giving place to a quiet and semi-rational condition. On discontinuing the alkali the excited condition recurred, being readily recontrolled by repetition of the treatment. In spite of energetic measures for the elimination of toxins, the patient succumbed. Post-mortem examination showed that while the uterine cavity appeared healthy, the liver revealed multiple small areas of necrosis with hæmorrhages, indicating the severity of the accompanying toxæmia.

The cause of the acidosis undoubtedly varies; in melancholics it is possibly due to intestinal fermentation, in dementia præcox probably due to some error of metabolism, while in one of our cases it was certainly due to prolonged diarrhœa.

REFERENCES.

- ¹ SHAW, J. J. M., *Jour. of Ment. Sci.*, 1914, July.
- ² GUIDI, *Ann. Instit. Psichiat. D. R. Univ. di Roma*, 1902-3.
- ³ SHAW, B. H., *Jour. of Ment. Sci.*, 1920, July.
- ⁴ WALKER, *Lancet*, 1921, May.

III.—SURFACE TENSION OF SERUM IN THE PSYCHOSES.

By C. LOVELL, LONDON.

Surface tension (S.T.) can be measured by the static or by the dynamic method. The static method has the advantage over the dynamic, in that it represents more closely the condition of the fluids

in the tissues. The S.T. of serum will be determined by a number of tension-reducing substances, and a number of tension-raising substances. All sera can be divided into eight groups, according to whether there is an excess or a deficiency of tension-lowering or of tension-raising substances; and whether these substances are toxic or non-toxic. At present we have to deal, practically, with four groups.

At the concave surface of the meniscus in a capillary tube, the surface film tends to diminish its total surface energy; the concentration of tension-lowering substances will increase in the film, and the concentration of tension-raising substances will decrease in the film. Hence we shall be measuring the excess or deficiency of toxic or non-toxic tension-reducing bodies. Immediately a capillary tube is set up in serum, the S.T.-reducing bodies begin to accumulate at the surface, and there is a steady decline of the meniscus. But after three hours the rate of decline is so slow that no change can be noticed in a quarter of an hour. Readings now taken will give a comparative estimate of S.T.-reducing bodies present.

An additional advantage of reading after three hours is that small differences of viscosity do not affect the result. We took as our standard a capillary tube of diameter 0.075 cm., which reduces the instrumental error to a minimum.

In the course of examining over three thousand cases, one has been much impressed by the small variation which exists in the S.T. value. It is not comparable, however, with the constancy of the H-ion concentration. The average S.T. value in a large number of normal individuals, mostly medical and engineering students, is 41.5 dynes per cm. There is a daily variation, the value being low in the evening. It can be altered slightly by diet, and more markedly by violent exercise. In places like University College Hall, where a number of normal individuals can be observed, a marked difference is noticeable between the mental activity of the students in the morning, when the S.T. is high, and in the evening, when it is low. Breakfast is a silent meal, dinner is the opposite. A low S.T., possibly the result of moderate fatigue, is associated with increased mental activity.

Preliminary animal experiments supported this theory. Animals in which the S.T. was raised by establishing a condition of hydræmic plethora all showed accumulation of fat, together with emphysema and various other changes.

At that time it was not possible to lower the S.T. of animals experimentally without killing the animal. Some non-toxic substances which lower the S.T. of water do not lower the S.T. of serum.

When we tested the theory on patients liable to convulsions, the results were not conclusive. For example :—

Mr. B. was a melancholic general paretic; his S.T. was 39·5 dynes. During a generalized fit it fell to 34 dynes. Two days later it was 36·5 dynes, and four days later it was 39·5 again.

Mr. S. was a chronic maniac; his S.T. was 33 dynes continuously. We know that the S.T. can be reduced by violent exercise, so the question arose as to whether the low S.T. caused the fit in the general paretic or whether the fit caused the low S.T.

Miss S. was an epileptic; after a fit her S.T. was 41·5 dynes. Later, she became hysterical and maniacal, and her S.T. then fell to 35·5 dynes.

Recently Dr. Farran Ridge, of Darenth, has supplied me with blood from patients subject to frequent and severe convulsions. Their S.Ts. are within normal limits.

Mr. S. was a case of acute mania. He was restless day and night; his S.T. was 42 dynes. While taking amylene hydrate he became quieter, and his S.T. was 48 dynes. When the drug was stopped he became restless again; S.T. 45 dynes. Again taking amylene hydrate he was quiet, and his S.T. was 49 dynes.

Now some students, by taking no food or drink all day, and spending the afternoon running over Hampstead Heath, reduced their S.Ts. to a minimum of 33 dynes. Therefore a low S.T. (*per se*) is not a cause of convulsions.

All forms of convulsion do not cause a low S.T. So far, nearly all convulsions in general paretics have been associated with a low S.T., as also have some forms of maniacal excitement. There are some cases, physically quiet, perhaps lying still in bed all day, who are mentally very active, talking incessantly day and night. Some of these cases have been examined; the S.T. ranges about 39 or 40, quite within normal limits.

The melancholics mostly had a high S.T., 44 or 45 dynes being the average. Some of the agitated melancholics, however, were lower.

Acute confusional cases are high; they become higher if they pass into stupor, and lower as they improve.

In general, cases of dementia præcox show no abnormality. But some cases diagnosed as dementia præcox have a high S.T. while they are resistive and inert, and as they return to normal the S.T. falls. Probably these latter are cases of acute confusional insanity in the stuporose stage.

When the serum of a normal individual is heated, the S.T., as indicated by the statical method, rises. The average range is 4 dynes, but may be as much as 8 dynes.

In our series of 114 cases, in only 5 cases was the range increased. These were :—

	Cases		Cases
Melancholia	1	Dementia præcox	1
Manic-depressive insanity	1	Dementia	1
Paranoia	1		

Thirty-nine patients showed a range, on heating, which was either very low or even reversed; that is, the S.T. was lower after heating. These were :—

	Cases		Cases
Dementia paranoides	5	General paralysis	1
Dementia præcox	6	Paranoia	1
Melancholia	6	Mania	2
Psychasthenia	8	Epilepsy	2
Confusional insanity	4	Various	3
Manic-depressive insanity	1		

If we take normal serum and divide it into two parts, and heat one part to 56° C. for half an hour and then cool it, and put equal quantities of the two specimens into collodion sacs and dialyse against distilled water, there is a great difference in the behaviour of the two specimens. In general the unheated specimen takes up water and loses little salt, whereas the heated specimen takes up little water but loses much salt. If we repeat this experiment, using a serum of which the S.T. variation on heating is small, the two specimens behave nearly or quite alike on dialysis. Thus there appears to be a difference in the union of the electrolytes and proteins in the two cases.

SUMMARY.

To compare the results of the complement and S.T. experiment, we may take 38 cases which had a range of S.T. on heating much below normal. This was associated with a low amount of complement in 23 cases, a high amount in 8, and 7 were in between. Cases with a high range of S.T. were too few for a comparison to be of value.

Of 28 cases examined more than once, it was found that where the range of S.T. was increased, the complement remained unaltered or was increased, never diminished.

Where the range of S.T. was unaltered, the complement remained unchanged in all but 3 cases of 11, where it was diminished.

A reduction of the range of S.T. in 9 cases was associated with no change of complement in 3, with a decrease in 4, and with an increase in 2 cases.

In general the complement varies with the range of S.T., increasing in amount as the range of S.T. increases, decreasing as it decreases, but always tending to remain a more constant factor.

The range of S.T. was always small in the psychasthenics.

The S.T. reading of unheated serum shows little variation in widely differing diseases.

In mental disease, dementia præcox shows no abnormality, but stuporose confusional cases show a high S.T.

Generally, cases with a low range of S.T. have also a low complementary power, and the combination of their electrolytes and protein in the serum differ from the normal.