Hitler showed this in Germany in one setting, and the Beatles recently did so again in this country in another. But such powerful methods prove of little use in helping the ordinary run of severely neurotic patients.

I am sure the answer lies in the fact that most severe neurotics and most mentally ill patients are not half as suggestible as, say, the ordinary medically ill patient and the ordinary medical student in a teaching hospital. We have made the great mistake, both in medicine and in psychiatry, of thinking that the psychiatrically ill should be more suggestible than the normal, instead of being generally much less so. But one quickly sees this if only the trouble is taken to examine the hypothesis in such a general teaching hospital. Here one sees the ease with which the normal patient, dying with cancer, can be reassured by the medical or surgical consultant that there is nothing very much at all the matter with him. One contrasts this with the difficulty the same consultant has when truthfully trying to make the healthy cardiac neurotic believe that he is going to live out the rest of the day. The anger of general physicians and general practitioners with the neurotic and the mentally ill is so often aroused because they will not swallow the "line of talk" so successful with all the rest of their patients and the medical students as well.

In *Battle for the Mind* (Sargant, 1957) and other papers (Sargant, 1949, 1951) I have tried to summarize all the research that brought me to the conclusion that psychotherapeutic techniques creating faith and increasing suggestibility in the normal can indeed make such people believe that they are even able to move mountains. But the same methods cannot usually make the neurotic phobic patient cross the road without renewed panic. It is this other research interest of mine which enables me to round off realistically what may have seemed at first, to some, to be too one-sided a treatment approach.

Conclusions

It seems that psychiatric patients are usually ill because there are components to their mental state, and an abnormal brain function which stops them, temporarily or permanently, showing the normal degrees of suggestibility essential for the ever-varying adaptation of the whole normal man to his changing environment.

Physical treatments seem able to restore the brain's normal flexibility, and so make it normally suggestible and adaptable again.

The Victorians were probably right when they thought that the main function of doctoring, and even of philosophic and religious doctoring, was to produce a *mens sana in corpore sano*. This means, however, that the mind must often be made well again so as to be able to benefit from the valuable lessons that can be taught to it by our philosophers and priests. But we have to produce a *mens sana* in the mentally and neurotically ill by treatment of the brain itself. We must stop thinking that the mind of the "whole man" can be made *sana* simply by treating some theoretically disturbed metaphysical humours and vapours, or warring super-egos, egos, and ids ; or that the psyche can, so to speak, be made to pull itself up by its own metaphysical bootstraps. This in the past has been the great mistake of doctors, psychiatrists, and even men of God when treating the psychiatrically ill in or out of hospitals of all kinds. They have forgotten what we have had to learn again and again in the past 15 years at St. Thomas's—namely, that brain function can best be brought to normal in exactly the same way that bodily functions have most easily been brought back to normal. And that is by modern empirical, mechanistic, and physiological treatments. Only after this has been done can one set about treating and trying to help the "whole man" with any hope of success. As the great Dr. Samuel Johnson—himself a victim of recurrent melancholia—so aptly put it: "Stay [with me] till I am well, and *then* you shall tell me how to cure myself."

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Mineral Metabolism, Mania, and Melancholia*

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"For the consideration is double, either how, and how farre the humours and affects of the bodie doe alter or work upon the minde ; or againe, how and how farre the passions, or apprehensions of the mind doe alter or work upon the bodie."—FRANCIS BACON (1561–1626).

An increasing understanding of the mechanisms underlying mental illness is coming from psychological, psycho-analytical, sociological, biochemical, and other fields of study. Probably some disciplines will contribute more to the comprehension of one illness, and others will add more to another. The affective disorders may be an example of this, as there is strong evidence that they have a predominantly biochemical basis. This evidence neither devalues nor excludes psychological factors, especially as bereavement and other psychic traumata are major aetiological factors in some patients who develop affective disorders. However, once established, the fact that the affective illnesses respond to physical methods of treatment is in favour of a biochemical hypothesis. In addition, the association of

severe mood swings with endocrine upsets is now well established.

During the early trials of cortisone excessive dosage was often complicated by alterations in mood, and similar occurrences are not unusual in untreated Cushing's disease and hypoadrenalism. Puerperal depression and the appearance of affective disorders during the glandular upsets of the involution period need no amplification, but the interesting association of transient but severe depressive symptoms in 10% of normal women pre-menstrually is not so well known (Kessel and Coppen, 1963). Some of the powerful drugs now available may induce depression. Of these reserpine and its derivatives are the worst offenders, and adequate treatment of hypotension with this drug carries an appreciable risk of precipitating a severe depressive episode. Other physical factors may give rise to affective disorders. These include virus infections, and a common example is post-influenzal depression. Despite all these associations, to establish a biochemical abnormality or constellation of abnormalities as the cause of a psychiatric illness, and to confirm that they are not just secondary occurrences, will be extremely difficult, as concurrence of events is no proof of a causal relationship.

If it is accepted that affective disorders are biochemically determined, then a reasonable working hypothesis is that they are the result of complex reversible changes in the pattern of brain excitability, which tend to be self-perpetuating for a period of time. Between these rather naïve statements and established knowledge of brain physiology is a large gulf, which the advances of the last two decades have narrowed slightly, and which may enable us to study mental illness from the physiological and biochemical viewpoints. These discoveries, made by Hodgkin, Huxley, and other physiologists, are contained in the ionic hypothesis of cell excitability. This hypothesis explains in part how ionic equilibria are achieved across the cell membrane, and how they are utilized by excitable cells to fulfil their functions.

Measurement of Ionic Patterns

Are mental illnesses caused by changes in brain excitability resulting from alteration in cell electrolytes ? Clearly it would not be possible to study individual brain cells, but if there are abnormalities in all cells in the body the problem of measuring ionic patterns is not impracticable, since this can be done by isotope methods.

Methods

All the methods for doing this depend on the isotope-dilution principle, which is similar to that used in the measurement of plasma volume with dye. A measured amount of isotope is given and allowed to mix thoroughly in the body. Suppose bromine-82 is used. This distributes itself in the extracellular space, and if a sample (plasma) is taken from this space, then the dilution of radioactivity in the sample (ratio of radioactivity in the body over radioactivity in 1 ml. of plasma) is a measure of the extracellular water (E.C.W.).[1] By the same token radioactive water (^3H_2O) can be used to estimate total body water (T.B.W.). The body does not discriminate between radioactive and non-radioactive water, and the tritiated[2] variety spreads rapidly and homogeneously throughout the body. If it were found that 1 ml. of water obtained from blood or urine contained 1/30,000 of the radioactive water remaining in the body when the sample was taken, then the T.B.W. would be 30,000 ml., or 30 litres. Of course in all these tests allowances have to be made for losses of radioactivity from the body. This is measured, and is subtracted from the known administered dosage to give the amount of radioactivity in the body when the test is completed.

[1] See glossary of terms (p. 267).
[2] Tritium is ^3H.

In a way similar to the estimation of E.C.W. and T.B.W., it is possible to measure the metabolically active sodium in the body—the " exchangeable sodium " (Na_E). The principle is the same as in the measurement of volumes, but the concept is more difficult to describe and visualize. A known amount of a radioactive isotope of sodium (either ^{22}Na or ^{24}Na) is allowed to equilibrate in the body, and a sample of plasma or urine is collected after a given interval. From this sample the radioactivity per milliequivalent of sodium (specific activity) is determined, and exchangeable sodium is given by radioactivity in the body divided by specific activity.

$$Na_E = \frac{\text{Radioactivity in body}}{\text{Radioactivity in sample}} \times \text{mEq Na in sample (mEq)}$$

The sodium pool, or exchangeable sodium, is not a simple entity but contains fractions with different properties. For instance, if an isotope of sodium is allowed to equilibrate for 24 hours before samples are taken, then the " 24-hour exchangeable sodium " comprises sodium in the E.C.W., sodium in the cells, and rapidly exchanging bone sodium. However, with ^{22}Na, which has a half-life of over two years, it is possible to wait for more than 24 hours, and then another fraction of body sodium can be demonstrated. Exchangeable sodium can be measured daily, and it can be seen increasing gradually over seven to eight days by about 10%. After this it reaches a plateau value, which does not alter with time. It is likely that this extra fraction of 10% in total exchangeable sodium is in the crystalline matrix of bone. Even total exchangeable sodium is only about 80% of the total body sodium, 20% being permanently inaccessible or metabolically inactive.

With the three isotopes—^{24}Na, ^{82}Br, and ^3H_2O—exchangeable sodium, T.B.W., and E.C.W. are obtained simultaneously, and by difference between T.B.W. and E.C.W. the intracellular water volume (I.C.W.) is calculated. It is not necessary to give radioactive isotopes to gain access to the potassium pool because there is a naturally occurring radioactive isotope, ^{40}K, already present in all potassium. This occurs in concentrations of 0.012%, and by measuring the activity due to this isotope in a highly sensitive whole-body counter the total body potassium (K_T) can be estimated. This can be added to the parameters available from the multiple isotope method, and further values are derived from the concentrations of sodium, chloride, and potassium in the plasma. The product of plasma concentration of sodium and E.C.W. is the absolute amount of sodium in the extracellular space (Na_{Out}), and a similar calculation gives the potassium in the extracellular space (K_{Out}). The difference between Na_E and Na_{Out} is termed residual sodium (Na_R), and represents the sodium in cells and the small amount of rapidly exchanging sodium in bone. Na_R is the nearest approach to intracellular sodium we can achieve by this type of technique, and the ratio $[Na_{Out}]/[Na_R]$ the nearest to the ratio of average concentrations of sodium across the cell membrane. Similarly K_T can be split into an extracellular moiety (K_{Out}), and, since there is negligible potassium in bone, into a residual fraction which can be labelled intracellular (K_{In}). The ratio $[K]_{In}/[K]_{Out}$ gives a better measure of the concentrations of this cation across the cell membrane than that obtained for sodium.

Thus what has been done by the physiologists for individual cells and tissues is accomplished for the whole body, so that an overall picture or " average " values for the electrolytes in the various compartments can be studied.

Electrolyte in Affective Disorders

Recent studies of the metabolism of electrolytes in affective disorders did not start with this type of investigation. Klein and Nunn (1945), Ström-Olsen and Weil-Malherbe (1958), Crammer (1959), and others estimated electrolyte and water losses during cyclical manic-depressive illness. Unfortunately no characteristic pattern corresponding to the various phases of the illness could be identified in different subjects. However, Margerison, Anderson, Dawson, and Lettich (1962) were able to demonstrate significant relationships between measures of the degree of verbal retardation in depressed patients and both the sodium/potassium ratio in the urine and specified frequencies in the E.E.G. In a later study Anderson, Dawson, and Margerison (1964) found that certain E.E.G. frequencies were

also related to changes in both sodium balance and the concentration of sodium in the plasma in depression.

Sodium Excretion in Depression

Further interest was stimulated by Schottstaedt, Grace, and Wolff (1956) when they reported decreased excretion of sodium in normal individuals during periods of depression. Isotopes were used first in the study of depression by Gibbons (1960), who estimated 24-hour exchangeable sodium and exchangeable potassium. An initial test was made shortly after admission to the ward, and was repeated after recovery. He was not able to demonstrate any significant differences in potassium, but the mean exchangeable sodium was 9% less on the second occasion. In patients who did not recover exchangeable sodium did not change. This work seemed to support the idea that there was sodium retention in depression, but the findings could have been caused by alterations in the size or behaviour of the normally non-exchanging or slowly exchanging sodium pools. At about this time Coppen (1960) published the finding that the penetration of ^{24}Na into the cerebrospinal fluid was about half the rate of that in normal subjects and in those who had recovered from their illness. This suggested that in at least one system sodium metabolism was abnormal.

Russell (1960) made careful sodium-balance studies in a group of depressed patients. He found a transient retention of water and sodium on the days of electric convulsion therapy (E.C.T.), but over the course of the whole illness there appeared to be no overall gains or losses. The discrepancy between this work and that of Gibbons could be reconciled only if the behaviour of exchangeable sodium were altered in depression, and Coppen, Shaw, and Mangoni (1962) pursued this problem further by using the long-life isotope of sodium ^{22}Na. After receiving 10 μc ^{22}Na all that was required of the patients was that they should sit in a whole-body counter for one to two minutes each morning, and should give a sample of urine. The body counter was calibrated against a standard each day, and the fraction of the dose of ^{22}Na remaining in the body was obtained from these two counts. The exchangeable sodium was calculated from the radioactivity remaining divided by the specific activity of the sodium in the urine specimen.

As in normal subjects, daily estimates of Na_E showed that this value increased by almost 8% over six to seven days and then reached a plateau level. This showed that slowly exchanging bone sodium had not been lost in depression. Subsequently the plateau figure at seven days was used as a starting-point and the exchangeable sodium did not alter thereafter until the time when the experiment was stopped, seven days after the last E.C.T. (Table I). Our results supported Russell's data rather than those of Gibbons. These differences between our work and the findings of Gibbons may lie in the fact that we were more interested in the acute changes occurring during reversal of the depressive process, whereas Gibbons waited longer before completing his second test. It may be that after recovery from depression there are delayed readjustments in the magnitude of the 24-hour exchangeable sodium which were missed by our shorter experiment. This possibility is of particular interest in view of our subsequent findings. However, at this stage it appeared, on the basis of Russell's work and our own data, that during the acute changes of recovery from depression total body and total exchangeable sodium did not

TABLE I.—*Means of Total Exchangeable Sodium in Depression*

No. of Patients	Means of Total Exchangeable Sodium (mEq)		
	Before Treatment	During Treatment with E.C.T.	After Full Recovery
12	2,409	2,446	2,396

None of the means was significantly different. Data from Coppen *et al.* (1962).

alter. Since the slowly exchanging fraction in bone was intact, there could not be much alteration in the only remaining fraction, 24-hour exchangeable sodium, during the period of our observations.

Sodium and Potassium Distribution in Depressive Illness

There remained the more fascinating half of the experiment, which was to find out if sodium and potassium are altered in their distribution in severe depressive illness. We studied depressed patients a few days after admission and again one week after their last E.C.T. (Coppen and Shaw, 1963). K_T was measured at the Medical Research Council's Radiological Protection Service, and the other values were obtained by means of the multiple isotope technique described above. Paired results were collected in 23 patients, and we found that both T.B.W. and weight increased slightly in recovery, but the proportions between E.C.W. and I.C.W. were unchanged. Plasma concentrations of sodium, chloride, and potassium and plasma water were constant, and Na_E and Na_{Out} were not significantly different on the two occasions. The really striking finding of this study was the remarkable and highly significant fall in residual sodium from a mean of 550 mEq during depression to a mean of 370 mEq after recovery (Table II). That no differences were found between the means of exchangeable sodium and the means of sodium in the E.C.W. (Na_{Out}) was due to the fact that, although a reduction in Na_R was the common factor, it was achieved in different ways by different individuals. As a result of this there were no consistent trends in Na_E and Na_{Out}. This gives some credence to the reasons put forward for the differences between our findings and those of Gibbons.

TABLE II.—*Means of 24-hour Exchangeable Sodium and of Other Measured and Derived Values in Severe Depression*

No.	T.B.W. (l.)		E.C.W. (l.)		I.C.W. (l.)		Na$_E$ (mEq)		Na$_{Out}$ (mEq)		Na$_R$ (mEq)	
	D	R	D	R	D	R	D	R	D	R	D	R
23	35·1	36·3	15·2	15·7	19·9	20·6	2,690	2,590	2,140	2,220	550	370
P	< 0·05		< 0·01		N.S.		N.S.		N.S.		< 0·001	

D = Depressed phase. R = After full recovery. N.S. = No significant difference between means.
Data from Coppen and Shaw (1963).

Total body potassium and intracellular potassium did not change in their absolute amounts (Table III). Since these data were published Moore, Olesen, McMurrey, Parker, Ball, and Boyden (1963) have published extensive body-composition data for normal subjects. By comparison with these individuals depressive patients were abnormal in several ways even after recovery from their illness. The ratio of I.C.W./E.C.W. was 1.31 in our patients, as compared with 1.04 in normal subjects (see Table VII). Since this ratio tends to fall with age and the normal individuals had a mean age lower than that of the patients, the difference between these two groups has, if anything, been minimized. Thus it seems that either E.C.W. was contracted or I.C.W. was expanded in subjects during depression and one week after their last treatment, and a similarly abnormal pattern of I.C.W./E.C.W. was found subsequently in manic patients (Coppen, Shaw, Malleson, and Costain, 1966). The other abnormality in depression was in potassium (Shaw and Coppen, 1966). Potassium is normally closely related to T.B.W., and when the potassium content of the body was assessed on the basis of T.B.W. the patients were found to be markedly deficient.[4] This was further illustrated by the means of K_{In} and the ratio K_{In}/K_{Out}, both of which were much below normal values (Table III).

[4] These figures are in the original paper, but only K_{In} and K_{In}/K_{Out} have been given here.

TABLE III.—*Means of Total Body Potassium and Other Values in Depressed and Normal Subjects*

Clinical State	No.	Age in Years	K_T (mEq)	K_{In} (mEq)	[K]In/ (mEq/l.)	[K]In/ [K]Out	Source of Data
A. Depressed patients	16	54·7	2,990	2,910	136	28·6	Shaw and Coppen (1966
B. Patients who have recovered from depression	14	55·5	2,980	2,890	132	27·6	,, ,, ,, (1963
C. Normal subjects	33	49·7			166	383·	Moore *et al.* (1963)
Significance of differences between means {A and B / A ,, C / B ,, C	N.S.	N.S.	N.S. <0·001 <0·001	N.S. <0·001 <0·001			

Methods

Because of the important implication of these results the methods require most careful examination to exclude artifacts. It is difficult to think of any systematic mistakes in the estimation of K_T and T.B.W. Methodological errors would tend to overestimate bromine space, and to explain the findings the bromine space must consistently underestimate E.C.W. The only anomaly likely to give rise to spuriously low E.C.W. values would be if cellular bromine were unusually low. Under normal conditions 7% of the bromine given enters red cells, 2% is in the gastro-intestinal tract, and less than 1% in somatic cells, and a correction of 0.9 is made to the bromine space to allow for this. A reduction in the small percentage entering the gut and somatic cells is both unlikely and unimportant in that it would have little effect on the estimation of E.C.W. However, the figure of 7% for red cells is an appreciable quantity, and if it were reduced from this to 1 or 2% it would almost halve the differences between depressed subjects and normal individuals.

In red cells there is a Gibbs-Donnan equilibrium across the cell membrane such that:

$$\frac{[Br]_{In}}{[Br]_{Out}} = \frac{[Cl]_{In}}{[Cl]_{Out}} = \frac{[HCO_3]_{In}}{[HCO_3]_{Out}} = \frac{[OH]_{In}}{[OH]_{Out}}$$

and these ratios are about equal to 0.7. If the ratio of distribution of bromine in the red cells is to alter there must be considerable change in the acid-base balance in the blood, and there is no evidence for this in depression (Challenger and Leyton, 1964).

As systemic artifacts in bromine space are improbable, then the findings are likely to be a true reflection of the overall electrolyte pattern in the body.

We have just completed a similar study in electrolyte distribution in 22 manic patients in collaboration with the M.R.C.'s Clinical Psychiatry Unit at Graylingwell Hospital (Coppen *et al.*, 1966). This was a more difficult study, chiefly because manic patients tend to discharge themselves prematurely, and also we were unable to measure K_T in these patients. To compensate for losses from the series we tested patients shortly after admission and again four weeks later irrespective of their clinical state, and assessed them on the day of the test by

TABLE IV.—*Water and Sodium Distribution in Depressed and Manic Patients*

Diagnosis	No.	*Excess or Deficit of Na_E as Predicted from T.B.W. (mEq)	Excess or Deficit of Na_R as Predicted from T.B.W. (mEq)	NaOut/ Na_R
Mania—manic phase	13	+ 345	+ 426	3·4
Mania—but in depressed mood when tested ..	9	− 136	+ 143	5·2
Mania—recovered	10	− 64	+ 63	6·3
Depression— depressed phase	23	+ 51	+ 179	4·3
Depression— recovered ..	23	− 133	− 17	9·9

* The derivation of these data is described fully in the original paper. Data from Coppen and Shaw (1963) and Coppen *et al.* (1966).

doctors' ratings and parts of the Hildreth scale. Manic patients change rapidly, and on the basis of the Hildreth scale they were split into groups according to whether they were in normal, manic, or depressed mood at the time of the biochemical test.

The results showed quite unequivocally that mania is associated with an increase in residual sodium but to a much more extreme degree than that found in depression (Tables IV and V). This is illustrated by the mean ratio of NaOut/NaR, which is 3.4 in manic patients, as compared with ratios of 4.3 and 9.9 in depressed patients and those who have recovered from depression respectively.

Physiological Effects of Lithium

There is no direct evidence to implicate electrolyte abnormalities as aetiological agents in affective disorders, but we have indirect evidence that ionic equilibria and mood may be closely associated from work we did in the actions of lithium. Lithium is effective in controlling the elevation of mood in mania (Maggs, 1963), and it is also known for its unique influence on sodium transport mechanisms (Schou, 1957). Lithium behaves like the sodium ion in that it can substitute for the latter in the production of an action potential, but once inside the cell its removal is much slower than that of sodium. Ultimately lithium accumulates in the cell membrane and sodium transport slows and may even come to a halt.

The bulk of knowledge about the physiological effects of lithium has come from short-term experiments at high concentrations. This in no way mimics the therapeutic situation, so we studied the effect of " normal " dosages of lithium, given for seven days, on the pattern of electrolyte distribution (Coppen, Malleson, and Shaw, 1965).

Multiple isotope studies were completed in eight patients before and after they received 1 g. of lithium carbonate a day for seven days. In four other subjects total body potassium was determined before and after taking lithium, and urinary losses of sodium, potassium, and chloride were estimated throughout.

We found that lithium did not alter the overall losses of these electrolytes in the urine and K_T remained constant. Plasma concentration of sodium, chloride, and potassium also did not change, but there was a profound derangement of ionic distribution (Table VI). Exchangeable sodium decreased by a mean of 620 mEq and the distribution volume of bromine rose by over 4 litres. If NaOut was calculated by using bromine space as a measure of E.C.W., then NaOut was sometimes greater than NaE, which was impossible. The isotopes were, technically speaking, still estimating NaE and the distribution volume of bromine, but these measures were no longer the same parameters which they had represented

TABLE V.—*Significance of the Differences Between the Means of the Groups in Table IV*

	1	2	3	4	1	2	3	4	1	2	3	4
1 Mania-manic phase ..	—				—				—			
2 Mania-depressed phase	0·002	—			0·05	—			N.S.	—		
3 Mania-recovered ..	0·01	N.S.	—		0·02	N.S.	—		0·02	N.S.	—	
4 Depression-depressed phase	0·05	N.S.	N.S.	—	0·02	N.S.	N.S.	—	N.S.	N.S.	0·05	—
5 Depression-recovered	0·001	N.S.	N.S.	0·02	0·001	N.S.	N.S.	0·001	0·02	N.S.	N.S.	0·005
	Excess or deficit NaE as predicted from T.B.W.				Excess or deficit Na_R as predicted from T.B.W.				NaOut/NaR			

C

TABLE VI.—*Effect of Lithium Carbonate on Distribution of Sodium*

	T.B.W. (l.)		E.C.W. (l.)		Na_E (mEq)		Na_Out (mEq)		Na_R (mEq)		Bromine Space (l.)	
	B	A	B	A	B	A	B	A	B	A	B	A
Means	35·2	37·1	15·7	20·0	3,290	2,670	2,260	2,820	1,030	−150	17·4	22·2
P	<0·05		<0·001		0·01		<0·001		<0·001		<0·001	

B = Before taking lithium carbonate. A = After taking lithium carbonate 1 g./day for seven days. Data from Coppen, Malleson, and Shaw (1965)

under normal conditions. The most likely explanation for our results was that there was an increase in the amount of bromine in the cells, and that the exchange of sodium across the cell membrane was so slowed that, 24 hours after giving the isotope, it was still incompletely equilibrated.

This experiment showed that lithium alters electrolyte distribution, and it seemed possible that its therapeutic actions could be related to its effects on the ionic pattern.

Conclusions

To summarize, it appeared from our work that residual sodium (cellular plus a small amount of bone sodium) was increased in depression and was even more abnormal in mania. By the time mood had returned to normal the residual sodium was also within normal limits. Patients in both groups of disorder either lacked E.C.W. or had an excess of I.C.W., and in depression cellular potassium was depleted. The water content of plasma and concentrations of sodium, potassium, and chloride in the plasma remained remarkably constant, and in no way reflected the severe underlying ionic disturbances. Lithium, a substance which has specific effects on mood in mania, disturbed sodium transport mechanisms and caused increased cellular penetration by bromine.

Discussion

This brief outline shows that the biochemical changes in affective disorders are gross to a degree seen up to now only in advanced cancer and similar wasting diseases (Moore *et al.*, 1963), and in extreme endocrine abnormalities (Coppen and Shaw, unpublished observations).

Comparatively little is known about the ways in which cellular electrolyte equilibria are maintained. In part they depend on the maintenance of normal permeability characteristics of the membrane, but they are also influenced by the energy mechanisms for extruding sodium. Neither of these two groups of factors is understood in any detail. If permeability is normal and there are no cation changes in E.C.W., the ionic equilibria are dependent on the " set point " of the concentration of intracellular sodium, and the mechanisms determining this are not understood. Likely candidates for influencing electrolyte equilibria are antidiuretic hormone, cortisol, aldosterone, corticosterone, and progesterone ; and Woodbury (1958) has shown that cortisol can affect the ionic content of brain cells. It is surprising that little is known about the effects of aldosterone on cation distribution.

It is possible, however, to discuss the ways in which these changes might affect excitable cells. For the degree of abnormality observed to be detected by a multiple-isotope method means that most of the cells in the body must be involved. Since the greater bulk of the cells in the body are muscle, this tissue must be included, and let us suppose for the moment that central-nervous-system tissue is also implicated.

The magnitude of an action potential approaches the equilibrium potential for sodium, and if we assume that all Na_R is intracellular and that change in Na_R involves the cells, then the figures for [Na]_Out and [Na_R] (Table VII) can be used for this calculation. It is given by the Nernst equation :

$$E = \frac{RT}{F} \ln \frac{[Na]_{Out}}{[Na]_{In}} \text{ millivolts}$$

where R = the gas constant, T = absolute temperature, F = the Faraday, and [Na_R] is the nearest we can get to [Na]_In and is substituted for this value in the equation.

TABLE VII.—*Concentrations of Sodium Across the Cell Membrane Assuming Na_R = Na_In*

Clinical State	No.	Source of Data	I.C.W./ E.C.W.	[Na_R] (mEq/l.)	[Na]_Out [Na_R]
A. Depressed ..	23	Coppen and Shaw (1963, 1965)	1·31	28·7	5·66
B. Patients who have recovered from depression	19	Coppen and Shaw (1963, 1965)	1·31	21·3	8·06
C. Normal subjects	33	Moore *et al.* (1963)	1·04	20.8	7·39
Significance of differences between means {A and B, A and C, B and C}			N.S. <0·001 <0·001	<0·05 <0·001 N.S.	<0·02 <0·005 N.S.

The average action potential in depression would be 7 millivolts less than that of normal subjects, and in manic patients the action potentials would be even lower than in depressed subjects. The amount of transmitter substance liberated by neurones at the neuro-muscular junction is proportional to the magnitude of the action potential. If this applies to the central nervous system as a whole and if these figures present an approximate measure of action potentials, then manic and depressed subjects will have " less active " synapses than normal people.

The situation is very complex, because not only is there a reversible change in sodium but there is also a constant low cellular potassium, which does not become normal with recovery. This must involve muscle, but we have no evidence of whether brain cells are similarly affected. If they are, then their resting potentials are again shown by the Nernst equation:

$$E = \frac{RT}{F} \ln \frac{[K]_{In}}{[K]_{Out}} \text{ millivolts}$$

([K]_In/[K]_Out values are given in Table III).

On the basis of the above equation the depressed subjects would have an " average " resting potential of about 8 millivolts below that of normal subjects, and therefore their neurones would be more excitable. At first glance 8 millivolts does not appear to be large in comparison to the action and resting potentials, but it should be remembered that this difference is of similar magnitude to the excitatory post-synaptic potentials which initiate depolarization at the synapses.

Thus there may be an intricate change in brain function compounded of more excitable neurones which, however, liberate less transmitter substance. There are no means of knowing how this would affect brain function.

Of course this type of speculation should be inadmissible, since it requires far more assumptions than are justified on the basis of the data. In particular, we cannot say to what extent brain tissue participates in the ionic shifts demonstrated for the rest of the body, nor whether changes in Na_R represent alterations in cell sodium. We have only indirect indications of involvement of the central nervous system, in part from Coppen (1960), where he showed slow penetration of ²⁴Na into cerebrospinal fluid, and also from the recent work with evoked cortical potentials. In this technique peripheral stimuli—for example, electrical shock to the wrist—give an evoked response in the cortex, which can be detected by repeating this procedure many times with an averaging device. Shagass and Schwartz (1962, 1963) showed that for one stimulus at the wrist there was a steeper stimulus–response curve in depression than in normal subjects—that is, the pathway was more excitable. However, when two stimuli were given separated by a short

interval the second response was reduced in depression—that is, although the pathway concerned was more excitable, its rate of recovery was reduced. This sort of pattern of change in excitability could have arisen from electrolyte changes in the brain. While we were studying the effect of lithium on electrolytes Gartside, Lippold, and Meldrum (1966) measured evoked cortical potentials concurrently, and found that the cortical recovery to a second stimulus was reduced in a way similar to that seen in depression. Thus the pattern of cortical excitability seen in depression (as measured by evoked potentials) was reproduced by a substance which can modify mood.

Promising Leads for Further Study

It is obvious that all these biochemical and physiological approaches to depression are at too preliminary a stage for more than tentative hypotheses, but they are providing exciting and promising leads for further study. Even if our electrolyte findings were firmly established and involvement of the central nervous system were implicated nobody would suggest that they were the only aetiological factors in affective disorders. For instance, amine metabolism is abnormal in depression, and giving tryptophan with monoamine oxidase inhibitors is followed by rapid clinical recovery (Coppen, Shaw, Maileson, Eccleston, and Gundy, 1965 ; Coppen, Shaw, and Farrell, 1963). It is likely that electrolyte abnormalities are only one factor in a complex chain of interacting mechanisms underlying the affective disorders.

Are the physiological and biochemical events accompanying the affective illnesses primary or secondary phenomena ? How have they arisen, and how can they be reversed ? Even more promising, how can they be prevented from occurring ? Only further research can provide the answers.

Summary

The affective disorders may be manifestations of altered brain excitability which are produced by an abnormal distribution of sodium and potassium across the cell membranes of neurones. In "whole-body" studies residual sodium (cell sodium and a small amount of bone sodium) was increased by 50% in depression and by 200% in mania, and this returned to normal after recovery in both groups. The concentration of potassium in the cells was reduced in the depressed patients both during their illness and one week after recovery. The significance of these findings is discussed, but a full evaluation must await information on whether or not these results reflect what is happening in the brain.

Glossary of Terms

Several conventions are in use for the description of body composition parameters. In an attempt to avoid confusion the conven-

tion used by physiologists has been used throughout this essay. For instance, in discussions concerned with sodium in the extracellular space either $Na_{E.C.F.}$ or Na_{Out} could have been given, but the latter was chosen. Similarly, for concentration of sodium in the plasma $[Na]$, $[Na_S]$, and $[Na]_{Out}$ have all been used, but only the last-mentioned has been employed here. Square brackets denote concentration.

Term	Derivation	Abbreviation and Units
Weight	—	Wt. (kg.)
Total body water	—	T.B.W. (l.)
Extracellular water	Bromine space × 0·9	E.C.W. (l.)
Intracellular water	T.B.W.–E.C.W.	I.C.W. (l.)
Exchangeable sodium	—	Na_E (mEq)
Concentration of electrolytes in plasma	—	$[Na]_{Out}[K]_{out}$ etc. (m Eq/l.)
Sodium in extracellular space (and similarly for K_{Out})	$[Na]_{Out} \times E.C.W.$	Na_{Out} (mEq)
Residual sodium	Na_E–Na_{Out}	Na_R (mEq)
Total body potassium	—	K_T (mEq)
Intracellular potassium	K_T–K_{Out}	K_{In} (mEq)
,, ,, concentration	$\dfrac{K_{In}}{I.C.W.}$	$[K]_{In}$ (mEq/l.)
Average residual sodium concentration	$\dfrac{Na_R}{I.C.W.}$	$[Na_R]$ (mEq/l.)

In general, intracellular and extracellular concentrations of electrolytes are given as [ ]$_{Out}$ and [ ]$_{In}$ respectively. Most of the other values, such as ratios, are self-explanatory.

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