INTEREST in water and electrolyte metabolism in mental illness is not new, nor is it confined to depressive illness. In fact schizophrenic patients have been intensively studied and there have been, for example, reports of phasic variations in sodium excretion in the acute episodes of periodic catatonia (Gjessing, 1953) and of delayed diuretic response to a water load taken by mouth in chronic schizophrenic subjects (Pfister, 1937). The first studies in depressives derived from the old observation that the urinary output tended to be low in depressive and high in manic illness (Allers, 1914). The obvious explanation, that manic patients are often thirsty and drink more, was not thought to be the complete explanation in every case and, as we shall see, there is justification for this view.

The first thorough attempt to correlate variations in metabolism, including the excretion of water and sodium, with variations in mental illness was made by Gjessing (1932, 1953) in his famous studies of periodic catatonia. This is a rare condition in which attacks of stupor or excitement occur at regular and predictable intervals. Gjessing's patients were given a fixed intake of food and fluids for many months, so that a detailed balance study was made during several cycles of illness. Most depressive patients, however, either have only one attack of illness or have their attacks at long and quite irregular intervals. A very few patients suffer from rapid alternations of mood, a short period of elation and overactivity being followed by a similar period of depression and retardation, with perhaps a day or more of normal mood at some stage of the cycle. Such patients can obviously be studied in Gjessing's way—always provided that they will cooperate with the investigator. Only a handful of studies have been reported, but they are worth considering in some detail for the light they may throw on the possible metabolic accompaniments of the commoner and more prolonged depressive illnesses.

The most intensive study is that reported by Klein and Nunn (1945). Their patient, a man aged 67, had suffered from chronic depression for 14 years from the age of 51. Later his illness took the form of regular weekly cycles consisting of five days of depression and retardation and two days of elation and overactivity. Various autonomic changes accompanied the changes in mood: thus his pulse was slower and his blood pressure lower during the depressed phases. For a period of several months he was given a constant mixed diet, with a constant fluid intake, and 12-hourly urine collections were made. When biochemical investigations were in progress he was kept in bed. The findings of interest in the present context may be summarized as follows. During the depressive phases the patient retained sodium and water, which was excreted again during the manic phase. The daily volume of urine averaged 780 ml in the depressive and 1,670 ml in the manic phases, and the urinary excretion of sodium and chloride was increased by 60 to 70%, during mania. Potassium excretion was unrelated to mood change and the same was true of other urinary constituents (calcium, ammonia, phosphate and nitrogen). Daily blood samples were taken throughout three consecutive cycles but no variations in haematocrit or haemoglobin concentration were seen. The change in weight was in the direction expected—a gain of 0.9 to 1.3 kg. during depression which was promptly lost again during mania. More detailed study of the rate of urine flow during the change-over from depression to mania showed that an abrupt increase in urine flow actually preceded the mood change.

The second of the two cases reported by Crammer (1959) was very similar. The patient was a 49-year-old man with a regular six to seven day cycle for at least five years. Two days were spent in stupor and four in manic overactivity. On a constant intake of food and fluids this patient also showed retention of water and sodium and gain in weight during his depressed phase—about 225 mEq. of sodium and 1.75 kg. in weight. Polyuria and excretion of sodium followed during the overactive phase. Haemodilution during the stuporous period was indicated by appropriate fluctuations in packed cell volume. In this patient also there were no regular variations in the serum concentration or urinary excretion of potassium. Crammer observed that the magnitude of the weight gain varied directly with the amount of sodium in the diet. Thus the gain was only about 700 g. on a diet containing 15 mEq. of sodium a day, while fluid restriction (to 500 ml. a day) practically abolished the weight changes. It should be mentioned that none of these manœuvreurs had any effect on either the timing or the intensity of the mood change. Moreover the time relationship between mood and fluid retention was reversed after several months of treatment with
chlorpromazine. Then the peak of the sodium and weight loss occurred at the start of the inactive phase while most of the weight was regained after the beginning of the overactive phase.

Cases of such short and regular alternation, while highly convenient for the biochemical investigator, are both uncommon and uncharacteristic. The patient described by Klein and Nunn, for example, slept a great deal during his depressed phases, whereas the typical depressive complains of insomnia. There are a few published studies of patients with rather longer episodes of depression and mania. The first patient of Crammer (1956), a man of 48 with a six-week cycle, was studied through one complete cycle (including a fortnight of mania and a fortnight of depression) while on a constant intake of fluids but a quite variable food intake. This patient lost weight during the first few days of his period of depression, thus behaving in a manner opposite to that of the two cases already discussed. Study of Crammer's graph shows that the weight loss was due to diuresis of water and sodium on two days only and that during the rest of the depressive phase sodium output was less than in the manic phase. The lack of control of the patient's diet makes it difficult to evaluate the findings. As will be mentioned below, two diets of equal caloric value but different composition may have quite different effects on water and sodium excretion. On the other hand it must be conceded that Crammer's other patient still showed regular fluctuations in weight and urinary volume when his diet was uncontrolled. Klein (1950) also described a second case, a man of 40 with recurrent attacks of depression and mania of varying duration. The depressive attack usually lasted about 13 days and the mania 18 days; the manic phase was followed by about 14 days of normal mood. This patient also was kept in bed, with a constant intake of food and fluids, and various urinary and blood constituents were measured. There was no indication of fluid or electrolyte retention at any stage of the cycle, although the patient's ability to excrete a water load taken by mouth varied, as will be discussed below. A study by Ström-Olsen and Weil-Malherbe (1958) may also be mentioned, since they give brief details of a 30-year-old woman with two to three week phases of mania or depression and one to three days intervening normal mood. The periods of depression and elation were reported to coincide with minima and maxima of the total urinary volume and of the excretion of sodium and potassium. Since food and fluid intake were uncontrolled, however, too much should not be made of this case.

We may conclude that in some cases of short-lived alternating mania and depression changes in water and sodium excretion accompany the variations in mood. The exact time relationships probably vary in different patients or may be varied in the same patient by drugs. Such changes are not invariably seen and, particularly if they are slight, cannot be interpreted unless the patient is receiving a constant food and fluid intake. The constancy of food intake is important not only because different foodstuffs contain different amounts of water and electrolytes. It is well known that obese subjects lose weight less rapidly on a high carbohydrate diet than on a high protein and fat diet of equal calorie value. Russell (1952) has shown that this variation in weight loss occurs even though the amount of water and sodium in the diet is kept constant and that it is a result of a more positive sodium and water balance. Similar effects of high and low carbohydrate diets on water balance have been observed in normal subjects.

The conclusions drawn above are based on findings in only four patients and further studies of such patients will be of great interest. Changes of a similar type have also been reported in a rather larger number of patients suffering from periodic catatonia, an illness with a different clinical picture. In five patients receiving a constant intake sodium retention was noted during the phase of illness in all of them and water retention in three (Gjesing, 1953). Essentially similar changes were observed in the two cases reported by Rowntree and Kay (1952). Recurrent episodes of fluid retention have also been reported in association with psychological symptoms of organic type—clouding of consciousness, disorientation, etc. (Biemond, 1949; Broser, 1951). In these cases, however, there was evidence of structural disease of the brain and the psychological symptoms, quite different in type from mania or depression, may well have been due to water retention, itself in turn the result of disordered central nervous control of osmotic equilibrium. Disorders of electrolyte and water metabolism have in recent years been recognized as occasional complications of brain lesions and the subject has recently been reviewed by Gilbert and Glaser (1961).

When we turn to the more usual form of depressive illness we find a disorder of several weeks' or months' duration, often of slow onset, which may occur only once in the patient's lifetime. It is at once apparent that it is almost impossible to study any metabolic changes which may occur at the beginning of the illness. There are patients with fairly frequent although irregular episodes of depression and it may very occasionally be possible...
to observe such a patient at the beginning of an attack. Generally, however, the depressed patient is not seen until the illness has developed. At this stage one can make various biochemical measurements and see how they compare with normal values. It may be said at once that plasma electrolytes have long been known to be in the normal range in depressed patients (Altschule, 1953; McFarland and Goldstein, 1939). The same is true of electrolytes in the cerebrospinal fluid (Eichhorn, 1954) and also of total body sodium and potassium measured by isotope dilution (Gibbons, 1960; Coppen, Shaw and Mangoni, 1962).

Comparisons of groups of depressed patients and of subjects without mood disorder are unlikely to reveal any differences unless they are gross. Since the depressed patient usually recovers, however, it is possible to use him as his own control and compare findings in the phase of illness with those obtained when he is well again. In addition, repeated determinations of certain variables may be made during the process of recovery in the reasonable expectation that any persistent changes which developed at the beginning of the illness will be reversed at its end. If recovery is hastened by electrical convulsive treatment or by antidepressive drugs, it has also been demonstrated that any changes found are not merely artefacts of the treatment.

For example, if sodium retention is a feature of the early stages of depression, and if such retention persists during the illness, diuresis of sodium would be expected to accompany recovery. The situation is complicated of course by the fact that most depressives experience decrease in appetite, and some of them eat so little that they lose a considerable amount of weight. Malnutrition, if severe, is itself accompanied by considerable perturbations of electrolyte metabolism which will mask any that may be part of the syndrome of depression. Similarly recovery from depression is usually accompanied by restoration of the appetite to normal and consequent gain in weight. Studies of recovering depressed patients should therefore be restricted to those who are not severely malnourished and, in order to avoid confusion with the effects of increased food intake, should preferably be made with patients receiving a constant intake of food and fluids.

The present author (Gibbons, 1960) investigated a group of 24 adult patients who showed the clinical picture of so-called endogenous depression. Total exchangeable sodium was measured in all the patients with $^{24}\text{Na}$ and total exchangeable potassium in 13 patients with $^{42}\text{K}$. The results were all in the normal range and the mean values, expressed as mEq. per kg. of body weight, were 42.8 and 45.1 for sodium and potassium respectively in the male patients, 37.0 and 32.8 for the female. The estimations were repeated after several weeks, by which time 16 patients had recovered or improved considerably, while eight were scarcely changed in mood because of failure to respond to treatment (in most cases electroconvulsive treatment) or because of relapse after initial improvement. In the recovered group the mean change in exchangeable sodium was a highly significant decrease of about 200 mEq.—9% of the total—whereas in the control group the mean change, an increase of about 30 mEq., was not significant. No consistent change in total exchangeable potassium occurred. Dietary variations were not thought to be responsible for the difference between the two groups since both were nursed on the same metabolic ward, partook of the same diet and showed similar fluctuations in weight. Moreover ten of the patients received a constant diet throughout the period of the investigation and the same changes were seen in them—a decrease of some 200 mEq, in six who recovered, an increase of 40 mEq. in four who failed to do so—as in the series as a whole. The conclusion drawn at the time was that the results supported the hypothesis that depression is accompanied by retention of sodium, which is excreted during recovery.

The patients who received the constant diet were subjects of another investigation carried out by Russell (1960). Fifteen depressed patients in all were investigated by the metabolic balance technique for periods of two to five weeks, during which time they received electrical convulsive treatment (ECT); 11 patients recovered or improved considerably during the period of study. It was found that ECT usually, but not always, caused slight and quite transient retention of water and sodium. The mean amounts retained were approximately 150 ml. and 12 mEq.; the largest amounts in individual subjects were 450 ml. and 50 mEq. Essentially similar results were obtained when patients were subjected to a ‘mock’ ECT procedure in which atropine and intravenous barbiturate were administered but a convolution was not induced. These slight and transitory effects of ECT or, more probably, of the emotional reaction aroused by the procedure may be compared with the large increases in extracellular fluid, measured by the thiocyanate method, reported by Altschule, Ascoli and Tillotson (1949) in their patients after ECT. This clearly illustrates the importance of avoiding malnourished subjects in this type of work and also of maintaining control of diet. Another interesting finding reported by Russell (1960) is that improvement in the mental state of his patients was not accompanied by any gain in weight so long as the
calorie intake was kept constant; when the calorie intake was increased, a prompt gain in weight ensued.

The overall balance in water, sodium and potassium during 66 days of 'recovery' (i.e. periods when improvement in mental state was occurring) was compared with 66 days of 'illness' (periods before improvement had occurred). The group as a whole showed a slight loss of sodium during the period of recovery of 5.5 mEq per day. This finding was not statistically significant, but it was in fact of the direction and magnitude to be expected from the study of the present author (Gibbons, 1960) already referred to. When individual patients were considered, four of them actually showed a slight retention of sodium. Changes in water and potassium balance for the group as a whole were negligible, although one patient showed considerable water retention (300 ml. per day) and another even greater loss (430 ml.). Russell concluded that no substantial alteration in the balance of water and electrolytes occurs as a depressed patient recovers and that the main immediate cause of weight gain during recovery is an increased calorie intake resulting from an increase in appetite.

At this stage, then, an isotope dilution study suggested that recovery from depression was accompanied by loss of sodium while a metabolic study, carried out on several of the same patients, showed that if anything did occur it must be of very small magnitude from day to day. The problem was investigated further by Coppen and Shaw (1962), who studied 12 depressed patients, all of them seriously ill, with the isotope dilution method. They were able to use the long-lived radioisotope $^{22}$Na, which is administered to the patient on one occasion only. Several days are allowed for full equilibration to occur and then the total exchangeable sodium can be measured daily for several weeks by determining the specific activity of sodium in plasma or urine. The necessary correction for radiosodium lost from the body presents no difficulty since the amount remaining is easily measured by a whole-body counter. The $^{22}$Na technique will detect smaller changes in total body sodium and will also show exactly when any changes occur. In fact Coppen and Shaw found no overall change in sodium during recovery and the mean change for the group was infinitesimal. Their finding is at first sight at direct odds with the present writer's work, but the two results can become compatible if it be supposed that there is no real change in body sodium but that changes occur in the amount of body sodium which equilibrates rapidly with ingested radiosodium. Normally most of the sodium in bone equilibrates only very slowly with radiosodium. If mixing occurred more rapidly during depressive illness, then an estimation of total exchangeable sodium at 24 hours would give a higher value during the illness than after recovery. It must be admitted that this sounds a rather far-fetched explanation, but the point is worthy of further investigation. Further work is in fact being carried out by Dr. Coppen and his colleagues, who are also measuring total body water and extracellular water in their patients. Their findings will be awaited with great interest. The same investigators will also have data on the body content of $^{42}$K, the naturally occurring radioisotope of potassium. Its estimation gives a reliable measurement of the actual total body potassium, not merely that fraction which is readily exchangeable with ingested potassium. It will be interesting to see if results with this technique support the conclusions of the present author and of Russell that no significant change in potassium balance occurs in depressed patients.

Some previous measurements of extracellular fluid (ECF) by the thiocyanate method may be mentioned here. Altschule and Tillotson (1956) found ECF values in depressed patients in the lower part of the normal range with an increase, still within the normal range, after treatment. Dawson, Hullin and Crocket (1956) found rather high values during healthy phases in four patients with mood swings, with a reduction in ECF in association with both manic and depressive phases. How far the changes were a result of variations in food or fluid intake is not clear.

There is some evidence that the sodium ion is handled rather differently during depressive illness. Coppen (1960) measured the rate of entry of radiosodium ($^{22}$Na) into the lumber cerebrospinal fluid (CSF) after rapid intravenous injection and found that this rate was lower in depressed patients than in a control group (patients before surgical operations) or in a group of schizophrenic patients or in a group of patients who had recovered from depression. The determination of the rate of entry requires repeated blood sampling during the first hour. When the more usual one-hour ratio was calculated (i.e. the concentration of radiosodium in the CSF expressed as a percentage of its concentration in the plasma at one hour after injection) exactly similar differences were found between the depressives and the other groups. The mean values were 2.7 for the depressives, 3.9 for the controls, 4.0 for the schizophrenics, 3.8 for the recovered depressives. There were no differences, however, in the rate of entry of radioactive water from plasma to lumber CSF. The author, while not claiming that the changes in sodium entry were related to the causes of depression, pointed out that ECT, an
effective method of treatment of depression, has been shown to increase the permeability of the blood brain barrier.

An attempt to confirm this interesting work has recently been made by a group in Edinburgh (Fotherby, Ashcroft, Affleck and Forest, 1962) who measured the one hour CSF-plasma ratio of radiosodium. They failed to find any significant difference between a group of 12 depressive patients and groups of 14 schizophrenic patients and seven patients with organic brain disease; the mean values were 3.5, 3.4 and 4.4, respectively. It may be significant that the four lowest values were found in depressive patients. Moreover the mean ratio was only 2.4 in the four patients who were suffering from severe ‘endogenous’ depression in fairly pure form. There was greater variation from patient to patient than in Coppen’s series. It should be noted that almost all the Edinburgh patients, unlike Coppen’s, were receiving phenothiazine drugs. It appears that the only way to settle the discrepancy between the two investigations will be to measure sodium entry in the same patients during illness and after recovery. If a change in the blood-CSF barrier is an important feature of recovery this method will show it without need for controls, whether of schizophrenics (who are not immune from depression of mood) or of normal subjects (who are still liable to undergo emotional turmoil).

Certain aspects of water metabolism have from time to time been studied in depressives. Lange (1928) mentioned how he had carried out oral water loading tests in depressed patients some years previously and had several times observed a delayed diuretic response. He presented a graph from one patient with a delayed response during illness and a normal response after recovery. Hoff and Pötzl (1930) also found delayed diuresis in seven out of eight depressives (while two manic patients showed a normal response). They also reported that posterior pituitary extract had less than the expected degree of antidiuretic activity in depressives. After recovery from depression the response to a water load was normal. Similar observations were reported by Altschule and Tillotson (1949). Thorvardsson (1942) also found a delayed diuretic response in nine severely depressed patients; when the test was repeated, however, after the patients had had an adequate fluid intake (1,500 ml) for several days, a normal response was found. He concluded that the delay in diuresis was merely a manifestation of dehydration, consequent upon the failure of the severe depressive to take enough to drink. This explanation may not be the whole one, however, because the manic-depressive patient reported by Klein (1950) received a constant diet with a con-

stant and adequate amount of fluid and yet showed a delayed diuretic response to a water load during his depressive phases and a brisk diuresis during his elated phases. It may be that in some depressives it is not so much a question of dehydration as of delayed absorption of large quantities of water.

Trolle (1945) reported an investigation into water excretion by 14 depressed patients in which he concluded that recovery may be accompanied by an increase or a decrease in the volume of urine, the change persisting for about a month. Graphs were presented of four patients who had received a constant diet and fluid intake: in two cases urinary volume increased and in two it decreased by 100 to 300 ml. per day. These findings may be compared with those of Russell (1960) referred to above. No data of electrolyte excretion are given. Trolle did not think that the variations could be explained by changes in motor activity, although an explanation on these lines might be constructed. On the other hand Trolle’s work might be an indication that different patients react differently and a warning that an attempt to find a constant pattern of electrolyte metabolism may be a pursuit of a will-o’-the-wisp. It is also conceivable that variations occur according to the type of the depression—if it be allowed that there are types of depression—or according to the presence or absence of certain clinical features. Thus Anderson and Dawson (1962) reported that about half of a series of 98 depressives had a high blood level of acetyl-methyl carbinol (AMC). There was a strong correlation between AMC level and certain clinical features, especially slow and hesitant speech and preoccupation with depressive ideas. The interest that this observation has for us at the moment lies in the fact that one of the determinants of a high blood level of AMC is an increase in intracellular sodium concentration.

Finally we may refer to the observations of Büssow (1950), who administered water and vaso-pressin to manic-depressive patients in order to produce water retention. Most of the depressive patients became temporarily worse and several manic patients became almost stuporous or lapsed into a transient depressive state. A colleague of Büssow (Karstens, 1951) repeated the manoeuvre in six healthy subjects and reported that the psychological effects resembled the symptoms of depressive illness.

The investigations reviewed above provide suggestive but equivocal evidence of some derangement of water and sodium metabolism in depressive illness. If further work establishes that derangements frequently occur, there remains the question of the relationship between the change in mood and the metabolic changes.
Some authors (for example, Crammer, 1959) have suggested that abnormalities in electrolyte metabolism may cause mood changes, at least in occasional cases. It is customary to refer to the work of Woodbury, who reported that the change in brain excitability produced in experimental animals by the administration of steroid hormones was the result of changes in the concentration of intra- and extracellular sodium in the brain (Woodbury, Timiras and Vernadakis, 1957). Moreover fluctuations in brain excitability, measured by the photoconvulsive technique, have been demonstrated to accompany variations in mental state in patients with recurrent catatonic stupor (Leiberman and Hoenig, 1953) while fluctuations in water and electrolyte excretion are a feature of periodic catatonia. Unfortunately for this line of argument, however, no abnormality in brain excitability could be detected when the photoconvulsive threshold was measured in a series of depressive patients (Driver and Eilenberg, 1960). It is true that reports of experimental depletion of electrolytes in otherwise healthy subjects speak of lethargy or apathy as notable symptoms (McCance, 1936; Fourman, 1954). These subjects, however, had lost a considerable proportion of their body stores of sodium or potassium, while it is clear that depressed patients show no significant depletion of these electrolytes. Similarly the observations of Büssow and of Karstens, that forced water retention makes depressives worse and healthy subjects depressed, cast no light on the pathogenesis of depression since the depressed patient is obviously not overhydrated. The notion that water and sodium retention may somehow cause depression of mood is also to be found in the doctrine that such retention causes premenstrual tension—a prototypic syndrome in which depression is one of the most characteristic symptoms—and that the disorder may be successfully treated with diuretics. (See, for example, Greene and Dalton, 1953). It may be mentioned here that it has yet to be demonstrated that the occurrence of premenstrual physiological symptoms is regularly accompanied by significant water and sodium retention. A recent balance study in the Metabolic Unit of this hospital failed to demonstrate it in a group of psychoneurotic women who complained of severe premenstrual exacerbation of their psychological symptoms (Bruce and Russell, 1962). Similarly an investigation of normal young women with $^{22}$Na failed to show the premenstrual retention of sodium which is often spoken of as if it were a quite usual phenomenon (Klein and Carey, 1957).

It seems much more likely that any electrolyte changes in depression are secondary effects of the illness. Some may be due to changes in the amount or composition of the diet or to variations in motor activity. Others may be the result of the emotional disturbance itself. It is well known that emotional upset can cause an increased or decreased rate of urine flow in human subjects (Chalmers and Lewis, 1951; Miles and Wardener, 1953). Moreover increased adrenocortical activity, which might lead to variations in electrolyte excretion, is known to occur in most cases of severe depression (Board, Wadeson and Persky, 1957, Gibbons and McHugh, 1962). There is also one study, which deserves to be repeated because of its great theoretical interest, which claims to show that different varieties of emotional experience, whether induced naturally by life experience or artificially contrived in the laboratory, are associated with different patterns of renal excretion of water and electrolytes (Schottstaedt, Grace and Wolff, 1956). In particular depression of mood is accompanied by retention of salt and water. This might then be the physiological counterpart of the changes noted by Klein and Nunn (1945) and by Crammer (1958) in their patients with cyclic manic-depressive psychosis.

Summary

A review of investigations on electrolyte metabolism in depressive illness suggests the following conclusions.

1. In some cases of rapid alternation of mania and depression variations in water and sodium metabolism accompany the fluctuations in mood.

2. In the more usual single attacks of depressive illness the metabolic balance technique failed to reveal such variation, but various studies with radiosodium indicate that there may be some alteration in sodium metabolism.

3. Changes in water metabolism have been found in some cases. They may be partly explained in terms of changes in fluid intake, and in all investigations of this type dietary control is important.

4. Changes in water and electrolyte metabolism which cannot be explained as the result of alternation in diet or activity are more likely to be the effect rather than the cause of the mood change.

I should like to thank Dr. Coppen, Dr. Forrest and Dr. Russell for allowing me to cite papers awaiting publication.

REFERENCES


GIBBONS: Electrolytes and Depressive Illness


Fotherby, P. R., Ashcroft, G. W., Affleck, J. W., and Forrest, A. D. (1962): 'Studies on Sodium Transfer and 5-Hydroxyindoles in Depressive Illness' (to be published).


—and (1962): The Effect of Diets of Different Composition on Weight Loss, Water and Sodium Balance in Obese Patients, Ibid., 22, 260.


