comparisons between the treatments are unbiased and independent of any general trend in scores, which applies to all treatment groups during the trial. From the clinician's viewpoint the results are bound to be regarded as somewhat less satisfactory.

It is obvious that, taken as a whole, the anticipated clinical course of multiple sclerosis is not one of clinical improvement, and from this point of view the standard of measurement we have employed in these trials has failed us. In seeking the reasons for these anomalous results the short duration of the gammaglobulin trial imposed on us by the limited availability of the substance should be noted. The tonic effect of any new form of treatment in a chronic disease is notorious, and six months might well not be long enough for such a non-specific psychological effect to be dissipated by subsequent disappointment.

The clinical examinations in the two trials were carried out by two different observers, but the observer was the same throughout each trial, and it is improbable that the mean improvement observed in treated and control patients in each trial was due to an overall simultaneous change in the standard of scoring of both observers. Again, a placebo effect seems to be the likeliest explanation: in a chronic and fluctuating disease, where the subjective component of the patient's disablement represents a variable moiety of the total incapacity, the detailed interest and attention shown and the rituals attendant on taking part in such a trial often have a striking effect on the patient's attitude towards his disability. Such a patient not infrequently carried out activities previously thought to be quite beyond his capacity. We believe that such factors probably account for the results described above.

Most of our previous trials have covered longer periods of time, when the inexorable progression of the organic process inevitably comes to outweigh the subjective effects of early optimism. In one such trial (Miller *et al.*, 1961a) re-examination after six months did fail to reveal any significant deterioration in both control and treated cases, though we have not previously encountered the slight clinical improvement observed here. It should also be mentioned that the doctors and nurses engaged in treating and examining the patients in the present study were an entirely different group from those concerned in previous trials and may well have exuded more optimism. The therapeutic effect of suggestive measures in chronic disease is the basis of a great deal of unorthodox treatment in these disorders, and it is unfortunate that our observations could be used to furnish ammunition for the view that at the present time—possibly with the solitary exception of corticotrophin in acute episodes of the disease (Miller *et al.*, 1961b)—treatment with inert substances accompanied by suggestion has at least as much to offer as any of the more rational lines of therapy which we have tried during the past few years.

Summary

Two separate controlled therapeutic trials are reported. The first, employing 57 patients, was designed to measure the effects of dosage with chloroquine (250 mg. daily) and also with soluble calcium aspirin (54 g. (3.5 g.) daily) on the clinical course of multiple sclerosis over a period of 14 months. The second, employing 21 female patients, was designed to measure the effect of 500 mg. of gammaglobulin, given intramuscularly at fortnightly intervals, on the course of the disease during a six-months period. Disability was scored numerically and clinical examinations were carried out by an observer unaware of the patient's treatment group. In the dosages and over the respective periods involved none of these three substances could be shown to influence the clinical course of the disease. The only patients who showed assessable deterioration during these two observations were those on chloroquine, who deteriorated by 13.3 points over a 14-months period.

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MINERAL METABOLISM IN MELANCHOLIA

BY

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This paper describes changes in the distribution of sodium between cells and the extracellular space in depressive illness. The work is a sequel to our previous investigations, which suggested that there may be important electrolyte abnormalities in this condition.

Physiological research has established the fundamental importance of electrolytes in the functioning of the cell. According to the ionic hypothesis the generation and propagation of impulses in neurones and other excitable tissues is dependent on the distribution of sodium, potassium, and other ions between the cell and its surrounding medium. The availability of radioactive isotopes of these ions has given an added impetus to research in this field, and great interest has been focused on sodium and its transport across cell membranes. These vital processes can be studied *in vivo* by applying radioisotope techniques to clinical investigations.

Aspects of sodium metabolism have been studied by measuring the mass of sodium in the body ("exchangeable sodium") which will mix or "exchange" with a tracer dose of radioactive sodium. An increasing amount of body sodium exchanges with the isotope over several days, and measurements are usually taken 24 hours after giving the isotope ("24-hour exchangeable sodium") or after allowing full equilibration of the isotope ("total exchangeable sodium"). The total exchangeable sodium is about 20% less than the body content of sodium and about 10% more than the 24-hour exchangeable sodium in normal

subjects. Gibbons (1960) showed that the 24-hour exchangeable sodium was significantly greater in depression than after recovery, but balance studies (Russell, 1960) and estimates of total exchangeable sodium (Coppen, Shaw and Mangoni, 1962) suggested that overall sodium metabolism was not affected in this illness. Coppen (1960) studied the rate of transfer of sodium across the blood-brain barrier. He reported a reduction in the rate of transfer of sodium from plasma to cerebrospinal fluid, which returned to normal when the patient had recovered. As these investigations suggest that any derangements of sodium metabolism in depression must lie in the readily exchanging fraction of body sodium or in the distribution of sodium between the various compartments of the body we have continued our investigations by measuring these and related parameters.

Methods

The pattern of distribution of water, sodium, potassium, and chloride was determined in depressed subjects before and after recovery from their illness. We employed an isotope dilution technique, using ^{24}Na, ^{82}Br, and tritium, and whole-body counting to estimate the total body potassium.

Patients and Timing of Investigations

The subjects were suffering from severe unremitting depression, diagnosed on a history of profound depression accompanied to a greater or less extent by other symptoms such as feelings of guilt and unworthiness; suicidal thoughts; loss of energy, interest, and concentration; depersonalization; insomnia; and loss of appetite. Patients who had had electric convulsion therapy (E.C.T.) within one month, tranquillizing drugs or monoamine oxidase inhibitors within two weeks, and those suffering from physical illness, severe malnutrition, or dehydration, were excluded.

The normal ward diet was given, with supplements of 186 g. of "complan" in 850 ml. of milk daily in three divided doses for two or three days before starting the investigation. The patients were kept up and about, and activity in the ward was encouraged, especially during the 24 hours of the investigation.

Most of the patients were treated by E.C.T., preceded by atropine sulphate (0.65 mg.) and anaesthesia with intravenous sodium thiopentone (125–200 mg.) and suxamethonium chloride (25–30 mg.). A few patients were treated with tranylcypromine or imipramine. Since the findings in these subjects were not different from those given E.C.T. they have been included with the other results. Initial studies were made a few days after admission and were repeated a minimum of six days after the last E.C.T.

Estimation of Total Body Potassium

Total body potassium was estimated on two occasions in 13 patients at the Medical Research Council's Radiological Protection Service, Belmont, Sutton. The details of the method have been published elsewhere (Maycock, Terry, Vennart, and Wise, 1960), and involve counting body radioactivity due to ^{40}K for 60 minutes in a sensitive body-counter. Naturally occurring potassium contains 0.012% of the radioactive isotope of potassium ^{40}K. From a measurement of body radioactivity due to ^{40}K the total body potassium was estimated by comparison with a phantom model of the human body filled with known amounts of potassium chloride. The method gives results accurate to ± 260 mEq of potassium.

Estimation of Total Body Water, Bromide Space, and Exchangeable Sodium

Radioactive isotopes were prepared by the Isotope Division of A.E.R.E. (Harwell) every second week from "specpure" Na_2CO_3 and "analar" NH_4Br. The (^{24}Na) Na_2CO_3 was neutralized with 0.1 N HCl and was made to 15 ml. with 0.5% (w/v) NaCl solution. Samples of the stock solutions were diluted to an activity of 5 μc./ml. at the time of administration of the isotope to the patient. A volume of 3 ml. of 0.02 N sodium thiosulphate was added to the solid $NH_4Br(^{82}Br)$ and the solution was made up to 15 ml. with 0.5% (w/v) NaBr solution. Aliquots of stock ^{82}Br solution were diluted as required to give an activity of 2.5 μc./ml. at the time of administration. Tritiated water was diluted to an activity of 50 μc./ml.

Volumes of 10 ml. were pipetted from each of the diluted solutions of ^{24}Na, ^{82}Br, and tritiated water into plastic dose-containers to give doses of 50, 25, and 500 μc. respectively. The mixed solutions and three washings of the container were given to the patients orally, through a straw, at 9.30 a.m. on the day of the test.

Pairs of 50-ml. plastic centrifuge tubes used for the blood samples were heparinized by the addition of 0.2 ml. of a 1% (w/v) solution of calcium heparin, 50 units/mg. To one of these tubes was added 0.2 ml. of a 5% (w/v) solution of sodium bromide, and both tubes were dried in an oven at 80° C.

For 23 hours after ingesting the isotopes all urine passed by the patient was collected in a plastic bottle. One hour later a "spot" sample was passed direct (in the case of female patients through a plastic funnel) into another plastic container. Then 40 ml. of blood was taken from an antecubital vein and the sample was divided between two centrifuge tubes. These were agitated gently and were spun immediately at 1,200 *g* for five minutes. Plasma from the tube containing only calcium heparin was used for the estimation of the concentrations of sodium, potassium, and chloride, and plasma water. The plasma containing heparin and carrier bromide was used for all the other determinations.

The sodium concentrations of the "spot urine" and plasma, and potassium concentrations of plasma were determined in duplicate by means of an EEL flame photometer. Plasma chloride concentration was measured in duplicate by the method of Schales and Schales (1941).

^{24}Na and ^{82}Br were separated for counting with ion-exchange resins. Columns were prepared from glass tubing of 5.5 mm. internal diameter drawn out at one end to an internal diameter of 2 mm. This end was plugged with glass-wool. A 5-cm. length of small-bore rubber tubing was attached to the tapered end and a gate-clip was used to occlude the tubing.

The two resins used, "zeo-karb 225" (SCR 13) and "de-acidite FF" (SRA 69), were converted to their H^+ and OH^- forms respectively, and two columns of each were made for each estimation. The height of the columns was 25 cm. from the glass-wool plug, and each was washed through with six bed volumes of ion-free water. The two de-acidite FF columns were used for 13-ml. aliquots of the "23-hour-" urine and the "spot" urine samples, and the zeo-karb 225 columns were used for 13 ml. of the 23-hour urine and for 13 ml. of a 1:3 dilution of the plasma. To avoid "dilution" effects from the water in the column the gate-clip was opened to allow a very slow flow. When the water reached the top of the resin 7 ml. of the urine or diluted plasma was added to top of the column in 0.5-ml.

amounts which were allowed to drain through to resin bed level and were discarded. The remainder of each aliquot (6 ml.) was passed through the columns and the effluent was collected.

Estimations of tritium were made on the "spot" samples and the "23-hour" urine. When the test was repeated, a sample of urine was collected to measure the tritium remaining in the body from the previous test.

Tritiated water was extracted from the samples by distillation to dryness under reduced pressure and was collected in a "U" tube immersed in a freezing mixture of methanol and solid carbon dioxide.

All samples were counted for a minimum of 10,000 counts. Five-ml. samples containing either ^{24}Na or ^{82}Br were counted in a well scintillation counter. Tritium was estimated at room temperature, using a low-energy coincidence-counter. One-millilitre aliquots were pipetted into counting cuvettes and 14 ml. of liquid scintillator NE.220 (Nuclear Enterprises Ltd.) was added. The samples were kept in the dark for half an hour before being counted.

For the estimation of plasma water 10-ml. beakers were dried overnight in an oven at 80° C. and were allowed to cool in a desiccator. Duplicate 1-ml. aliquots were added to each of two beakers, using a grade A Ostwald pipette, and were then weighed on a single pan balance reading to ±0.1 mg. The beakers were then dried overnight in an oven at 105° C., were allowed to cool in a desiccator, and were reweighed. The coefficient of variation of repeated estimates of plasma water was 0.8%.

Packed cell volume was measured by centrifuging samples of heparinized blood (without carrier bromine) in haematocrit tubes for 30 minutes at 1,500 *g*.

The calculation of the data and of the values derived from the data has been described by Veall and Vetter (1958).

Estimated and Derived Values

Estimated Values	*Units*
Body weight (Wt)	kg.
24-hour exchangeable sodium (Na_E)	mEq
Distribution volume of bromine (DBr)	l.
Total body water (T.B.W.)	l.
Total body potassium (K_T)	mEq
Haematocrit	% (v/v)
Plasma water	% (w/v)
Concentration of electrolytes in plasma ([Na], [K], etc.)	mEq/l.

Derived Values	*Derivation*	*Units*
Extracellular space (E.C.F.)	DBr × 0.9	l.
Sodium in extracellular space ($Na_{E.C.F.}$)	[Na] × E.C.F.	mEq
Residual sodium (Na_R)	Na_E—$Na_{E.C.F.}$	mEq
Exchangeable chloride (Cl_E)	[Cl] × DBr	mEq
Intracellular water (I.C.W.)	T.B.W.—E.C.F.	l.
Potassium in extracellular space ($K_{E.C.F.}$)	[K] × E.C.F.	mEq
Residual potassium (K_R)	K_T—$K_{E.C.F.}$	mEq

TABLE I.—*Exchangeable Sodium and Other Measured and Derived Values*

Age (Years)	Sex	Body Weight (kg.)		T.B.W. (l.)		E.C.F. (l.)		I.C.W. (l.)		Cl_E (mEq)		Na_E (mEq)		$Na_{E.C.F.}$ (mEq)		Na_R (mEq)	
		D	R	D	R	D	R	D	R	D	R	D	R	D	R	D	R
60	F	58·4	58·3	31·9	38·0	15·7	14·0	16·2	24·0	1,860	1,720	3,180	2,530	2,420	2,020	760	510
47	M	81·5	83·85	48·8	52·2	19·7	20·6	29·1	31·6	2,410	2,450	3,690	3,810	2,800	2,930	890	880
41	M	58·0	60·5	30·8	36·2	14·5	16·7	16·3	19·5	1,670	1,950	2,640	2,680	2,030	2,590	610	90
62	F	58·15	61·45	28·2	33·0	13·2	12·4	15·0	20·6	1,620	1,500	2,770	2,410	2,030	1,740	740	670
64	F	52·65	56·45	33·8	32·1	15·4	16·4	18·4	15·7	1,780	1,870	2,730	3,030	2,220	2,360	510	670
57	M	48·5	50·0	33·1	33·9	13·3	14·0	19·8	19·9	1,510	1,640	2,590	2,330	1,890	1,960	700	370
51	M	57·1	56·5	39·6	39·5	15·9	16·7	23·7	22·8	1,820	1,980	2,830	2,890	2,260	2,450	570	440
76	M	57·2	57·6	34·3	37·5	15·6	15·6	18·7	21·9	1,710	1,780	3,190	2,750	2,290	2,180	900	570
47	F	61·0	64·4	33·4	31·6	13·1	14·3	20·3	17·3	1,510	1,620	2,180	2,120	1,790	1,930	390	190
63	F	49·0	51·3	30·5	31·9	15·1	14·6	15·4	16·3	1,730	1,750	2,550	2,350	2,140	2,120	410	230
50	F	48·5	47·6	26·4	28·5	11·1	11·2	15·3	17·3	1,290	1,240	1,710	1,600	1,550	1,550	160	50
45	M	76·4	73·5	42·4	46·0	18·3	18·4	24·1	27·6	2,150	21,20	3,010	3,130	2,470	2,580	540	550
59	F	85·5	84·75	39·4	38·2	16·3	18·6	23·1	19·6	1,900	2,190	3,180	3,370	2,350	2,680	830	690
65	F	49·0	50·8	27·1	26·0	12·2	13·1	14·9	12·9	1,420	1,550	2,190	2,380	1,760	1,860	430	520
46*	F	68·45	69·0	32·7	32·3	13·7	13·5	19·0	18·8	1,630	1,560	2,240	2,100	1,890	1,810	350	290
61†	F	54·4	58·9	34·9	36·3	16·6	16·0	18·3	20·3	1,970	1,830	3,050	2,310	2,360	2,190	690	120
74	F	49·9	53·5	27·0	29·9	13·6	14·9	13·4	15·0	1,570	1,700	2,360	2,200	1,900	2,040	460	160
49	F	55·8	60·2	29·4	33·9	13·7	14·1	15·7	19·8	1,610	1,680	2,480	2,250	1,970	1,970	510	280
68	M	68·5	67·8	37·2	36·1	15·5	16·3	21·7	19·8	1,670	1,830	2,400	2,310	2,050	2,230	350	80
52	F	46·7	47·6	29·9	28·3	11·6	12·7	18·3	15·6	1,340	1,470	2,010	2,060	1,620	1,740	390	320
48	M	67·6	67·9	48·0	50·1	19·1	20·9	28·9	29·2	2,250	2,410	3,260	3,320	2,670	2,860	590	460
54	M	74·55	75·0	42·0	40·0	18·2	18·5	23·8	21·5	2,080	2,140	2,980	2,840	2,510	2,630	470	210
39	M	81·4	78·3	45·6	44·7	17·3	18·5	28·3	26·2	2,040	2,110	2,710	2,870	2,250	2,630	460	240
Means 55·7		61·2	62·4	35·1	36·3	15·2	15·7	19·9	20·6	1,760	1,830	2,690	2,590	2,140	2,220	550	370
P		<0·05		<0·05		<0·01		N.S.		<0·02		N.S.		<0·1		<0·001	

D = Depressed phase. R = After clinical recovery. All patients treated with E.C.T. except *tranylcypromine (30 mg./day) and † imipramine (75 mg./day).

TABLE II.—*Means of Plasma Electrolyte Concentrations and of Values Derived from Data in Table I*

	Plasma Electrolyte Concentrations (mEq l.)			T.B.W.	DBr	I.C.W./E.C.F.	Cl_E	Na_E	Na_E M(10)	Na_E F(13)	$Na_{E.C.F.}$	Na_R	$Na_{E.C.F.}/Na_R$	$K_{E.C.F.}$ (mEq)
	Na	K	Cl	ml. kg.			mEq/kg. Body Weight							
Means in depressed phase	141	4·8	105	577	279	1·31	29·2	44·7	44·6	44·8	35·5	9·2	4·3	73
Means after recovery	141	4·8	105	585	282	1·31	29·6	41·8	43·5	40·5	35·8	6·0	9·9	75
P	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	<0·02	N.S.	<0·02	N.S.	<0·001	<0·005	N.S.

TABLE III.—*Exchangeable Sodium and Other Values in Subjects not Included in Tables I and II*

No.	Age (Years)	Sex	Treatment	Body Weight (kg.)		T.B.W. (l.)		E.C.F. (l.)		I.C.W. (l.)		Cl_E (mEq)		Na_E (mEq)		$Na_{E.C.F.}$ (mEq)		Na_R (mEq)		$Na_{E.C.F.}/Na_R$	
				1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd
1	59	F	None	69·75	—	35·1	—	15·1	—	20·0	—	1,760	—	2 160	—	2,160	—	440	—	4·9	—
2	37	M	"	65·8	—	41·3	—	16·3	—	25·0	—	1,880	—	2,820	—	2,340	—	480	—	4·9	—
3	62	F	E.C.T. imipramine	44·45	45·0	23·6	24·5	10·3	10·3	13·3	14·2	1,170	1,220	2,020	2,420	1,510	1,480	510	940	3·0	1·6
4	49	F	E.C.T.	66·4	65·8	30·8	31·2	13·1	14·5	17·7	16·7	1,530	1,710	2.250	2,310	1,930	1,990	320	320	6·0	6·2

Reason for exclusion from main series: Nos. 1 and 2, spontaneous recovery before first investigation made. No. 3, still depressed after E.C.T. No. 4, became manic after E.C.T.

TABLE IV.—*Values Obtained by Other Workers*

Authors	No. of Subjects Studied	Sex	Mean Age (Years)	Na_E (mEq/kg. Body Weight)	Na_R (mEq/kg. Body Weight)	K_E (mEq/kg. Body Weight)	Na_E/K_E	E.C.F.*	Remarks
McMurrey *et al.* (1958)	10	M	36·8	39·5	6·3	48·0	0·83	23·4	Normal subjects
	10	F	33·7	38·3	5·9	39·4	0·97	22·8	,, ,,
Flear *et al.* (1958)	—	M	—	41·6	—	46·8	—	—	Normal subjects. Data derived from a number of papers
	—	F	—	40·2	—	41·2	—	—	
Moore *et al.* (1956)	—	M	60	41	7·6	47	0·9	23·4	Numbers from which means derived not stated
	—	F	60	41	7·8	40	—	23·7	
	10	M	63	49·4	8·5	36·2	1·37	30·2	"Syndrome of depletion"

* Litres/kg. body weight × 100.

Other derived values include ratios—for example, $Na_{E.C.F.}/Na_R$ -and parameters expressed in terms of the body weight.

Results

The results are presented in Tables I–III and V–VII, and a list of values obtained by other workers is given in Table IV. Exchangeable sodium and total body potassium measurements have been made concurrently in eight subjects, and therefore some of their results have been included in both Tables I and II and Tables VI and VII.

TABLE V.—*Means of Haematocrit and Plasma Water Estimations*

	Packed Cell Volume (%)	Plasma Water (%, w/v)
Depressed phase	45·5	92·7
After recovery	44·3	92·6
Number	15	15
P	N.S.	N.S.

but neither change is statistically significant. The difference between the exchangeable and extracellular sodium is the "residual sodium" (Na_R), which falls from an initial level of 550 mEq to 370 mEq ($P<0.001$). This alteration in distribution of sodium is illustrated well by the ratio $Na_{E.C.F.}/Na_R$ (Table II) which is 4.3 during depression and 9.9 after recovery. We divided these results into those from patients who might be classified as "reactive" and those as "endogenous" depression, but the two groups show no significant difference.

By comparison with other workers' results (Table IV) the exchangeable sodium expressed as milliequivalents per kilogram of body weight (Table II) appears to be rather high during the depressive phase, but returns to a more normal value after recovery. If the figures are subdivided according to sex (10 male, 13 female) the male group change from 44.6 to 43.5 mEq/kg. (not significant) and the female patients from 44.8 to 40.5 mEq/kg. ($P<0.02$).

TABLE VI.—*Total Body Potassium and Other Measured and Derived Values*

Age (Years)	Sex	Body Weight (kg.) D	Body Weight (kg.) R	K_T (mEq) D	K_T (mEq) R	$K_{E.C.F.}$ (mEq) D	$K_{E.C.F.}$ (mEq) R	K_E (mEq) D	K_E (mEq) R	Na_E (mEq) D	Na_E (mEq) R
60	F	58·4	58·3	2,400	2,330	72	71	2,330	2,260	3,180	2,530
47	M	81·5	83·85	3,680	3,760	106	105	3,570	3,650	3,690	3,810
62	F	58·15	61·45	1,890	1,820	69	58	1,820	1,760	2,770	2,410
64	F	52·65	56·45	3,170	3,040	69	77	3,100	2,960	2,730	3,030
51	M	57·1	56·5	3,150	3,260	80	73	3,070	3,190	2,830	2,890
76	M	57·2	57·6	2,630	2,890	78	81	2,550	2,810	3,190	2,750
63	F	49·0	51·3	2,020	1,970	71	76	1,950	1,890	2,550	2,350
59	F	85·5	84·75	2,460	2,760	83	86	2,380	2,670	3,180	3,370
55	M	91·8	90·7	3,450	3,100	105	106	3,340	2,990		
42	F	59·0	63·0	2,860	3,400	69	73	2,790	3,330		
68	M	61·7	64·6	3,580	3,810	80	88	3,500	3,720		
59	M	67·1	68·7	3,630	3,530	86	96	35,40	3,430		
29	M	67·60	70·30	3,630	3,680	99	89	3,530	3,590		
Means 56·5		65·15	66·75	2,970	3,030	82	83	2,880	2,940	3,020	2,890
P		<0·01		N.S.		N.S.		N.S.		N.S.	

D = Depressed phase. R = After full clinical recovery. All treated with E.C.T.

TABLE VII.—*Means of Estimated Values and of Figures Derived from Total Body Potassium Data*

	K_T (mEq/kg. Body Weight)	$K_{E.C.F.}$ (mEq/kg. Body Weight)	K_E (mEq/kg. Body Weight)	K_T/T.B.W. (mEq/l.)	Na_E/K_T
Means in depressed phase ..	46·3	1·3	45·0	77·2	1·17
,, after recovery	46·0	1·3	44·7	76·3	1·08
P	N.S.	N.S.	N.S.	N.S.	N.S.

The increase in total body water (T.B.W.) of 1.2 l. is paralleled by a similar rise of weight of 1.2 kg. The extracellular fluid (E.C.F.) and intracellular water (I.C.W.) also rise with recovery, but the figures for I.C.W. are more scattered than those of E.C.F. and the difference in I.C.W. is not significant. However, the mean of the ratio of I.C.W./E.C.F. (Table II) is the same for the periods before and after treatment.

The most interesting findings of this investigation are in the sodium values (Tables I and II). The means of the total 24-hour exchangeable sodium figures fall and the means of extracellular sodium rise with clinical recovery,

The values in the male patients remain high after recovery. Residual sodium expressed in terms of body weight (6 mEq/kg.) after recovery is lower than the normal value. This trend is still present when the figures are subdivided according to sex—in the male patients Na_R is 5.9 (normal 7.6) and in the female 6.1 (normal 7.8).

As might be expected from the rise in E.C.F. on recovery, the exchangeable chloride is increased. This and the alterations in distribution of sodium have been produced while plasma water and the concentrations of sodium, potassium, and chloride in plasma remain constant (Tables II and V). The means of the values for total potassium, potassium in the E.C.F., residual potassium, and ratio of Na_E/K_T are not affected by the depressive process (Tables VI and VII). Values of Na_E/K_E are given in Table IV for comparison. Since K_T is smaller than K_E by a factor of about 8% (Remenchik and Miller, 1962), Na_E/K_E should be less than Na_E/K_T. It seems, therefore, that the mean of 1.08 is unusually high, but the number of results presented is small.

Discussion

This study has shown that electrolyte metabolism is abnormal in severe depression, and that the abnormality mainly affects sodium. In normal subjects about 40% of the total body sodium is in bone. Half of this bone sodium will not exchange, but a quarter will exchange rapidly in a matter of hours and the remainder is exchangeable over five to seven days (Veall and Vetter, 1958). This latter fraction is the slowly exchanging fraction of body sodium. It is similar in depression to that found in normal subjects, and the total body sodium does not change with recovery (Russell, 1960; Coppen *et al.*, 1962). In the present study there was no significant difference in the values of the 24-hour exchangeable sodium, so it follows from this that the only fraction of total body sodium remaining, the non-exchangeable bone sodium, also must remain virtually constant in depression during the period studied. The difference between our results and those of Gibbons (1960) may arise from the difference in timing of the second investigation. In Gibbons's series the mean interval between estimations was 44 days, whereas in our group the mean interval was 35 days.

The most significant abnormality we found was in the apparent difference in distribution of the 24-hour exchangeable sodium. The phrase "apparent difference" is used because there are several possible interpretations of the data. One source of difficulty stems from the estimation of the extracellular space, which is an important parameter because many values, including Na_R, are derived from it. There are advantages in using bromine to study this space (Staffurth and Birchall, 1960), but it should be emphasized that there is no completely satisfactory method of measuring extracellular space. Moreover, the volume of distribution of bromine, which is itself an electrolyte, may be affected by the metabolic processes in depression which produce an electrolyte change. In fact, the small rise in E.C.F. of 0.5 l. on recovery is insufficient to account for the reduction in residual sodium, even if this increase in E.C.F. were artifact.

It seems probable, therefore, that the distribution of sodium is altered in this illness. Assuming that this is so, then the difference in distribution of the 24-hour exchangeable sodium can be explained by one of two ways. The bulk of the 24-hour exchangeable sodium is in the extracellular space, but the remainder (Na_R) is in the intracellular compartment and in bone (the rapidly exchanging fraction of bone sodium). The decrease of 180 mEq of residual sodium upon recovery means that either exchangeable sodium in bone or intracellular sodium is increased in depression. At present we know little about factors which affect the amount of exchangeable sodium in bone, although there is evidence that adrenocortical hormones can do so (Nichols and Nichols, 1956; Arons, Nusimovich, Vanderlinde, and Thorne, 1958). As there are no methods for measuring intracellular or bone sodium directly in man which are not subject to considerable error, we must be content to conclude that residual sodium includes intracellular sodium and an unknown quantity of exchangeable sodium in the skeleton in crystalline form.

The regulation of the distribution of electrolytes between cells and E.C.F. is still imperfectly understood. The separation of sodium and potassium into extracellular and intracellular phases is of the greatest physiological importance. It is responsible for the potential difference (polarization) across the cell membrane, and a reversal in polarization is the means by which neurones and other excitable cells function. Any failure to maintain optimum levels of cations on either side of the cell membrane must affect the efficiency of the process. There are, however, few *in vivo* studies of the effects of modifying the distribution of cations on the function of the C.N.S. Woodbury (1958) and his co-workers have shown the importance of sodium in brain excitability. They found that cortisol lowered the electroshock threshold and that this was accompanied by increases in intracellular sodium. Deoxycortone had an opposite effect—sodium was withdrawn from the brain cells and brain excitability was reduced. Since there is evidence that adrenocortical activity is increased in depression (Persky, Grinker, Hamburg, Sabshin, Korshin, Basowitz, and Chevalier, 1956; Gibbons and McHugh, 1962) it is possible that high levels of cortisol could produce the pattern of sodium distribution reported in this paper.

Although an investigation by Driver and Eilenberg (1960) revealed no alteration in the photoconvulsive threshold in depression, a report by Shagass and Schwartz (1962) showed that the recovery of cortical excitability after an evoked potential was diminished in psychotic depression. This finding might well be associated with abnormal levels of intracellular cations. There are few systematic studies in the literature of other conditions using similar techniques to those employed in the present investigation. Moore, McMurrey, Parker, and Magnus (1956) described a "syndrome of depletion" which included several severe illnesses where there was a "chronic energy deficit" and cachexia. In many ways the electrolyte disturbances in depression are similar (Table IV). Twenty-four-hour exchangeable sodium and Na_R (both expressed in terms of body weight) are nearly as high as in the depletion syndrome, and the ratio of Na_x/K_E is similarly increased in depression.

The results from recovered depressive patients suggest that they may differ constitutionally from normal subjects. The ratio of Na_E/K_T appeared to be higher than normal, and in the male patients Na_E (mEq/kg. body weight) was higher than the values obtained by Moore *et al.* (1956) in normal people of about the same age-group. In both male and female patients the residual sodium is low after recovery.

It is not possible at this stage to say if the pattern of distribution of sodium in depression is causal to the development of this illness. We do know that it is not confined to depression, although in at least one condition in which sodium is similarly distributed—Cushing's syndrome—depression is a common symptom (Coppen and Shaw, 1962). The evidence from neurophysiology and from Woodbury's work certainly suggests that it is possible for alterations in the distribution of ions between neurones and E.C.F. to produce functional effects, but this work is too remote from the clinical manifestations of depression for useful speculation along these lines. We suggest that an evaluation of these findings must await an understanding of the metabolic factors responsible for the alteration in sodium distribution. By manipulating these variables it should be possible to see if they are important in the production of depression; if so, it should then be feasible, though difficult, to assess the role of these changes in sodium in altering brain function and producing neuropsychiatric symptoms.

In conclusion, we suggest that the present investigation provides evidence of a marked disturbance in the distribution of sodium during a depressive illness. These changes are mostly confined to residual sodium, which includes both

intracellular and exchangeable bone sodium. It is not possible on the evidence to say if the pattern of distribution of sodium is related causally in any way to the depressive syndrome, although there is evidence that alterations in brain intracellular sodium can affect brain function. After recovery from depression the pattern of sodium distribution suggests that there may be constitutional differences between depressive and normal subjects.

Summary

Water and electrolyte distribution in patients suffering from severe depression was studied by means of a multiple isotope technique and total body counting. Each patient was tested twice, initially when severely depressed and later after clinical recovery.

Residual sodium, which includes intracellular and some bone sodium, was very significantly increased during depression. Total exchangeable sodium and extracellular sodium did not change significantly. Total body water, extracellular fluid, and extracellular chloride were all greater after recovery. Estimates of total body potassium and residual and extracellular potassium did not vary; nor did plasma concentrations of sodium, potassium, chloride, plasma water, and haematocrit.

The abnormal proportion of exchangeable sodium to total body potassium, even after clinical recovery, suggests that depressed patients may differ constitutionally from normal subjects in this respect.

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ARTERIAL BRUITS IN ANAEMIA

BY

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Auscultation over arteries has in recent years acquired importance. A bruit over a limb may point to focal narrowing, due usually to atherosclerosis, or more rarely to an aneurysmal dilatation or to an arteriovenous communication. Peart and Rob (1960) found that 59 out of 103 cases of internal carotid artery stenosis had a systolic bruit over the bifurcation of the carotid artery. An identical bruit in this area may occasionally arise from stenosis of the origin of the external carotid artery (Matthews, 1961). A bruit over the subclavian artery may be an important pointer to a condition of stenosis leading to ischaemia in the arm or to brain-stem and cerebral ischaemia (Reivich *et al.*, 1961 ; North *et al.*, 1962). Forty-five per cent. of cases of renal artery stenosis leading to hypertension have a bruit over the affected renal artery (Brown *et al.*, 1960). Hunt *et al.* (1962) found a bruit in 18 out of 20 patients with non-atheromatous stenosing lesions of the renal arteries. A continuous bruit in the upper abdomen or flank is a feature of renal arteriovenous fistula (Abbott and Poutasse, 1961). Ranger and Spence (1962) described a case of stenosis of the superior mesenteric artery with a systolic bruit over the central abdomen and both groins. Forty-five per cent. of patients with aortic thrombosis have a murmur over the lower abdomen or lumbar vertebrae (Covey, 1955 ; Starer and Sutton, 1958).

Not all bruits are pathological. Osler (1880) and Still (1921) published papers on cephalic bruits in children. Wadia and Monckton (1957) found spontaneous intracranial bruits in 60% of healthy children aged 4–5 years, the incidence falling to 4% at 15–16 years. Chest and neck bruits were found in only 15 out of 513 children below the age of 15 years as compared with intracranial bruits in about 260 of the children. However, spontaneous intracranial or carotid bruits were heard in only 3 out of 228 adults. Bruits could be produced in about 20% of adults by contralateral carotid compression. This may happen also after carotid ligation (Matthews, 1961) and presumably thrombosis.

The following case in which carotid bruits due to anaemia contributed to an erroneous clinical diagnosis of intracranial angioma and led to unnecessary carotid angiography suggested this investigation into the incidence and site of arterial bruits in anaemia.

A 41-year-old housewife had been complaining for 20 months of a throbbing sensation in the left ear. It was synchronous with her pulse and was aggravated by exertion, stooping, leaning her head forwards, noise, emotion, and alcohol. It was relieved by lying down, leaning her head backwards, and pressure on the left side of the neck. For a number of years she had some swelling of the legs. A systolic bruit was audible along the length of both carotid arteries. It was louder in the upper half of the neck and was sometimes more marked on the left. A faint bruit was present over the eyeballs but there was none elsewhere over the skull. No thrill was palpable. Firm pressure over the lower part of the sternomastoid muscle on the left side caused rapid ballooning of the internal jugular vein in the left carotid triangle. This sign was described by Wadia (1960) as a very rare finding in 100 normal individuals and negative in only 1 out of 17 individuals with intracranial angiomata. The sign was negative on the right. There were no other positive findings except some ankle oedema. At a