SERUM CALCIUM IN PROLONGED NARCOSIS.

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Investigations into the possible causes of toxic symptoms arising during the course of prolonged somnifaine narcosis showed that a fall in serum calcium occurred during the course of the treatment (1). Previous investigations on blood calcium (3, 4, 5, 6, 15) made it clear that during barbiturate narcosis there was a fall of 10–20% of the normal value. Observations, however (7, 8, 9, 10), that therapeutic exhibition of insulin resulted in an increase in serum calcium suggested that no gross abnormality in calcium level was to be expected during the modified somnifaine-insulin-glucose treatment (2) practised in this hospital. The investigations here reported were undertaken to determine what fall in serum calcium occurred during this modified treatment, and to determine whether this fall was sufficient to cause toxic symptoms. If so the advisability of taking steps to avoid them could then be considered. The investigations showed a definite lowering in serum calcium during the course of treatment of psychotic patients by this method, and they suggested that somnifaine and insulin are only pseudo-antagonistic in their effect upon calcium metabolism. In the ten cases reported, a fall in serum calcium of from 3–20% has invariably been observed, the maximum being reached four to seven days after the beginning of the treatment.

Technique Employed.

The technique employed for the estimation of calcium was a modification of the Kramer-Tisdall method using trichloracetic acid as a protein precipitant. Calcium oxalate is precipitated from the protein-free filtrate of 2 c.c. serum, washed, dissolved in sulphuric acid and titrated with permanganate. Washing with saturated calcium oxalate, as suggested by Stanford and Wheatley and recommended by Peters and Van Slyke (11), was employed. It is commonly accepted that the major errors in the estimation occur during this washing of the precipitate, and in order that small differences in calcium concentration might justifiably be claimed as real, further modifications in the technique were considered necessary. Instead of the usual centrifuging

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and removal of the mother liquors by decantation, the estimation was made in a 10 c.c. filter tube fitted with a Jena sintered glass filter. Selected G. 4 filters were found to be impermeable to the oxalate precipitated after standing overnight. The liquid is prevented from passing through the filter by an air pressure of ½–1 atmosphere applied underneath. Air-bubbles may in this way be used for stirring. By applying suction the precipitate may be rendered almost free from mother liquor, thus permitting the use of saturated calcium oxalate as a washing fluid. The risk of obtaining high values due to precipitation of calcium oxalate (11) is so reduced as to be negligible. The tube is fitted with an outer hot-water jacket so that solution of the oxalate preciptate in N sulphuric acid and its titration with freshly prepared N/100 permanganate can readily be made in the same tube without transference. The end-point was estimated by adding slight excess of permanganate, cooling, addition of 5% KI, and titration with thiosulphate from a 0·1 m.l. microburette. A reproducibility in the results of ± 1% has been observed. The filter tubes must be kept in chromic sulphuric acid when not in use, and filtered air during suction is advisable as errors due to included dust particles may readily occur.

The investigations were on recent unselected admissions undergoing prolonged narcosis by somnifaine-insulin-glucose. Treatment was on the lines generally carried out here, viz., isolation of the patient in a darkened room; intramuscular injection of somnifaine 2 c.c. twice daily followed in each case by 10–20 units insulin subcutaneously and glucose *ad libitum* by the mouth. Careful watch was kept for the occurrence of any toxic symptoms. Apart from a mild transient acetonuria which is to be expected in a proportion of the cases, and which is always relieved by increased insulin, signs of acidosis were uniformly absent. Specimens of blood were taken at intervals as indicated and usually about three hours after a somnifaine injection and always prior to food.

To determine the effect of dietary fluctuations, four patients were fed on a milk diet for four days prior to and throughout the period of the treatment (Cases 1, 2, 3, 4). Two also received rectal glucose and nothing by mouth throughout the period (Cases 8, 9). One (Case 10) received somnifaine alone, without insulin or glucose. The occurrence of bradycardia, pulse-rate 56, led to cessation of the treatment in this case after six days. The remaining cases received a milk diet by mouth throughout the course of the treatment. In no case was any change in diet made until twenty-four hours after cessation of treatment.

The cases examined are shown in the following tables. An initial value of serum calcium was determined in each case just before beginning treatment. Deviations from this, prior to and during the treatment, in mgrm.% are shown in Table I, with the appropriate plus or minus sign as indicated.

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TABLE I.—*Variation from Initial Serum Calcium Level during Narcosis.*

Patient number.		Somnifaine treatment begins. ↓												Somnifaine treatment ceases. ↓		
1	Time in days	− 3	− 2	− 1	1	3	5	8	12	15	19			23	25	
	Change in serum calcium	− 0·36	− 0·04	− 0·20	− 0·26	− 0·54	− 0·31	− 0·58	− 1·36	− 0·64	− 0·29			+ 0·02	+ 0·26	
2	Time in days	− 3	− 1		1	3	5	9	13					16		
	Change in serum calcium	− 0·30	+ 0·10		− 0·50	− 0·62	− 0·72	− 0·54	− 0·42					− 0·02		
3	Time in days	− 3	− 2		1	4	6	8	10	12				15	17	
	Change in serum calcium	+ 0·20	+ 0·10		− 0·28	− 0·70	− 1·30	− 1·50	− 1·42	− 1·84				− 1·14	− 0·72	
4	Time in days	− 3	− 2	− 1	1	2	5	6	7	8	11			12	13	14
	Change in serum calcium	+ 0·08	+ 0·16	+ 0·10	− 0·38	− 0·80	− 1·18	− 1·00	− 0·88	− 1·12	− 0·64			− 0·04	+ 0·78	+ 0·68
5	Time in days	− 2			2	5	7	10						16	19	
	Change in serum calcium	− 0·21			− 1·06	− 0·62	− 0·24	− 1·05						+ 0·06	+ 0·70	
6	Time in days	− 1			2	5	9	12						13		
	Change in serum calcium	− 0·31			− 0·22	− 0·40	− 0·12	− 0·64						+ 0·35		
7	Time in days	− 1			2	5	11							16		
	Change in calcium serum	+ 0·14			− 0·72	− 0·94	− 0·82							− 0·10		
8	Time in days	− 2			2	6	9							11		
	Change in serum calcium	− 0·20			− 1·62	− 2·04	− 1·42							− 0·20		
9	Time in days	− 2			1	2								4		
	Change in serum calcium	+ 0·11			− 0·32	− 0·85								+ 0·42		
10	Time in days	..			1	2	3	4	5	6				8		
	Change in serum calcium	..			− 0·60	− 1·04	− 1·70	− 2·07	− 1·91	− 1·49				− 0·29		

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Details of the patient, the initial value of serum calcium and the maximum percentage fall in each case during the narcosis are shown in Table II.

TABLE II.

	Patient.	Sex.	Age.	Diagnosis.	Days of treatment.	Initial calcium level (mgm. %.).	Maximum percentage fall during narcosis.
1	A. K—	F.	42	Agitated melancholia	22	11·26	12
2	F. B—	M.	55	Mania	15	10·16	7
3	K. R—	M.	19	Schizophrenia	14	10·30	17
4	C. H—	F.	30	Melancholia	11	10·08	11
5	S. M—	M.	20	Schizophrenia	15	9·96	11
6	C. K—	F.	51	Melancholia	12	9·36	7
7	G. W—	F.	37	,,	15	10·88	9
8	A. B—	M.	33	Schizophrenia	9	11·20	18
9	M. G—	M.	20	Mania	3	9·82	9
10	W. H—	M.	18	Schizophrenia	6	10·91	19

All the cases examined show a fall in serum calcium averaging about 7% with an average maximum fall of 12%. This fall is followed by a fairly rapid return towards normal when the treatment ceases. If such a lowering in serum calcium were resultant upon a diminished calcium intake, which is unlikely (12), the seven patients on a continuous milk diet, where available calcium is high, would be expected to show a marked difference from those receiving no calcium during the period. This does not appear to be the case. Moreover, fluctuations of the order observed do not usually result from changes in dietary calcium (13), whereas the return towards normal before any change in diet has been made, particularly so in the case of the patients without food, does not suggest an effect due to a diminished availability of dietary calcium.

A lowered serum calcium may occur, however, after a prolonged period without food, since the serum protein becomes reduced and a decrease in the fraction of calcium bound to protein is then to be expected (14). The larger fall in serum calcium in Case 8 may indeed partly be explained on this basis, but, since patients on a milk diet also show a lowering in serum calcium during narcosis, it must be conceded that hyperproteinæmia and dietary factors do not largely contribute to the pathogenesis of the effect. The lowering in total serum calcium might be correlated with a lowering in non-protein bound or "ionized" calcium, such a lowering possibly being the result of consistent alkalosis during the narcosis. This, however, does not appear to be the case (6). Its interpretation would, then, lie in a more ready elimination of calcium in the urine or fæces during the narcosis, or in a diminished calcium mobilization from bone and other tissue—effects usually associated with a dysfunction of the parathyroids. For definite conclusions on this point further work is necessary on the therapeutic value of parathormone in somnifaine narcosis and on the effect of narcotic treatment on the total calcium balance of the body.

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It is necessary to point out here, however, that the relatively small fluctuations observed indicate no serious pathological disturbance in calcium metabolism and do not suggest any *necessary* modification in the somnifaine treatment when it is used in conjunction with insulin and glucose. In the only case examined (Case 10) without supplementary insulin and glucose the maximum fall (19%) occurs within four days of beginning the treatment. This approach towards the pathological suggests the necessity for some form of therapy to maintain calcium metabolism at normal during the narcosis, and is a reminder to those using prolonged narcosis, either with or without the Cardiff modification, that such a possibility should be borne in mind. While insulin may, at any rate partly, perform this function, the possible additional value of parathormone merits consideration.

Summary.

(1) In ten cases investigated under prolonged somnifaine-insulin-glucose narcosis an average maximum fall in serum calcium of 12% was observed.

(2) This effect is not dependent on dietary changes, nor is it great enough to warrant any serious modification of the treatment as already applied.

(3) Parathyroid dysfunction is suggested as causative and the possible therapeutic value of parathormone is considered.

(4) A modified technique for accurate calcium estimation is described.

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