THERAPEUTIC ATTEMPTS IN MANIC-DEPRESSIVE PSYCHOSIS.

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THE investigations on which is based the form of therapy presented in this paper being partly several years old, and partly published in Scandinavian languages, it will be of advantage to review them briefly.

Howell in 1905, and Zondek in 1920, besides others, claimed to have demonstrated similarity or identity in the action of the autonomic nerves and the Ca and K salts in the tissue fluids, and a number of publications have appeared, especially in Germany, during the past ten years, accepting this theory. If the theory were correct, deviations in these salts might be expected to be found in psychotic patients, where the autonomic innervation *a priori* should be altered, as in the affective psychoses. At that time (1922–23) comparatively reliable micro-methods were available for the estimation of serum calcium only. My first investigations were therefore limited to Ca estimations alone. These were made upon 200 mental patients besides a number of control subjects. Of the patients, practically only those showing affective disturbances showed alterations in the serum calcium. These alterations were partly in the form of increased or relatively high Ca-concentrations and partly as a more unstable Ca-level than in normal subjects, the variations from one day to the other being much more marked than under normal conditions, where the variations are very small. No other phenomena could be made responsible for the variations than the affective disturbance. A number of manic-depressive patients were followed up with daily estimations of Ca through several weeks, the nurses at the same time making graphic and written notes of their total impression of the state of the patients at the moment of venepuncture and of the course of the disease. An obvious correlation appeared between these Ca-estimations made by me and the graphic controls made by the nurses, so that the impression could not be avoided that on the whole a heightened emotional tone was accompanied by or preceded by an increase in serum calcium (Fig. 1).

By this time (1924) micro-methods for the estimations of K and Na were available, and these substances being the physiological antagonists of Ca, they were now studied in those cases where the alterations in Ca had been found.

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In serum potassium irregular fluctuations are found, partly increased, partly diminished values. In the case of serum sodium the variations are more uniform and pronounced, and practically always go in the opposite direction to the variations in Ca, i.e., besides the instability the tendency seems to be towards low values (Fig. 2). The Ca/Na ratio in serum, which is a ratio of considerable physiological importance, was therefore in a number of these cases found to be increased, and to a certain extent, as far as could be seen, parallel with the emotional tone of the patients (Fig. 3). During the past twelve years I have repeatedly had the opportunity to control and confirm these general results. A few other authors also have confirmed them, while still others

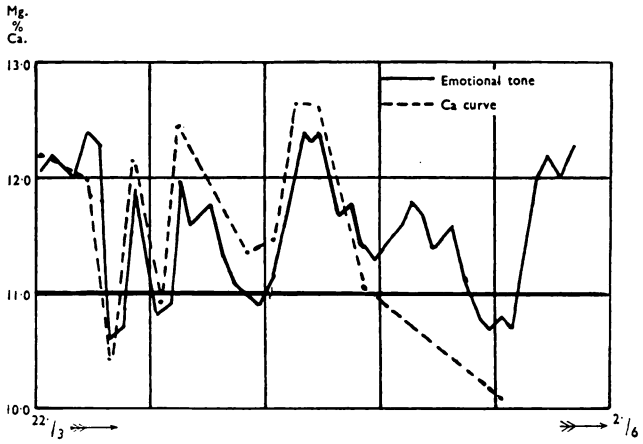

FIG. 1.

have not been able to confirm our results; so far as I know these have only published results based on single analyses of very few cases, with a technique which by some has been considered unreliable.

Clinical investigation of the state of the autonomic nervous system of these patients showed that there are a number of symptoms of autonomic disturbance to be found in their psychoses; these symptoms vary from one patient to another, from one moment to the next in the same patient. In no case could the unilateral preponderance of either the sympathetic or parasympathetic innervation on all the observed functions be detected (colour of face, pupils, bowel functions, sweating, pulse and oculo-cardiac reflex). This therefore sufficed to show that the alterations found in the electrolytes could not be interpreted according to the Howell-Zondek theory.

Pharmacological investigation of the peripheral autonomic cardio-vascular innervation by the atropine method of Danielopolu-Carniol (and other tests) seemed to point to a diminished peripheral innervation, sympathetic as well as parasympathetic in varying degrees. Of course the method can be criticized,

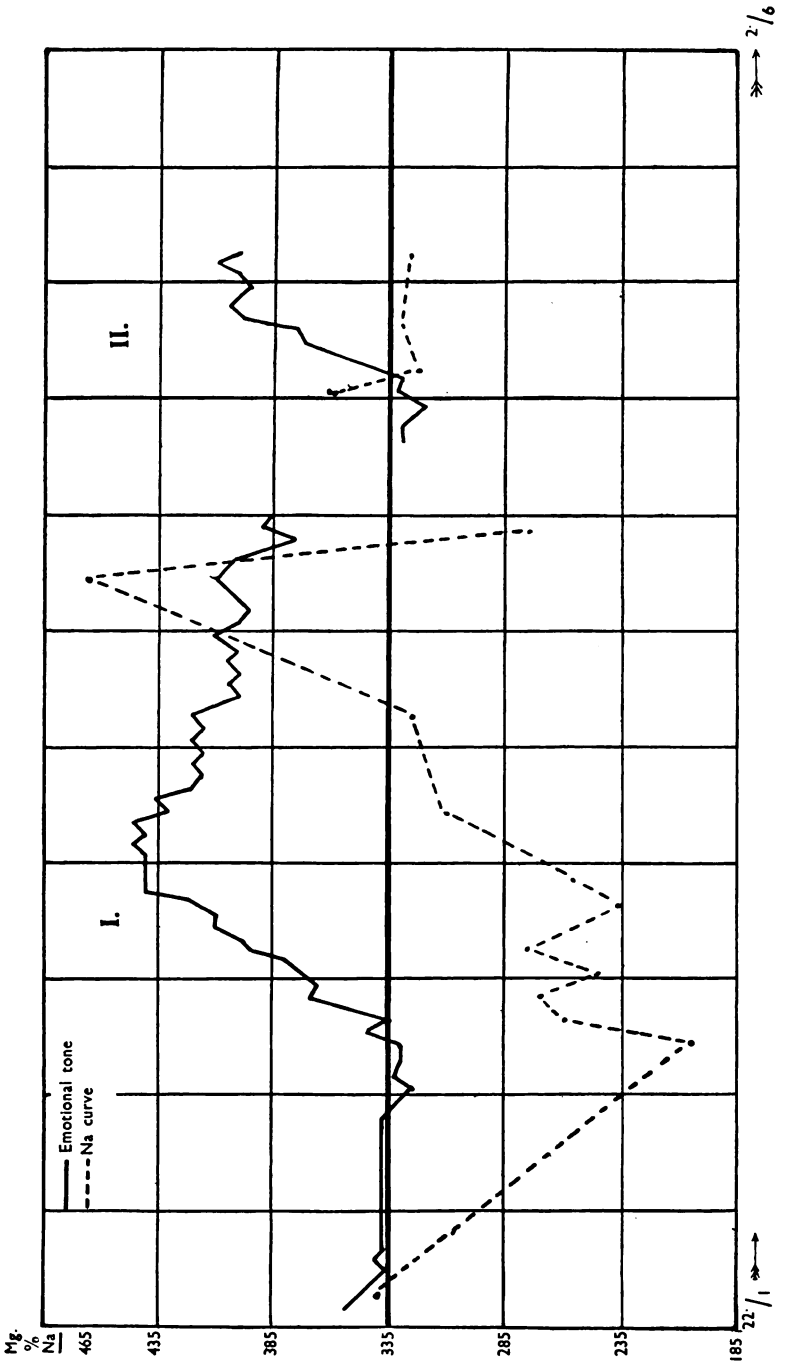

FIG 2.

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as it may be discussed how many factors influence it, etc., but nevertheless it does not seem to be so very much inferior to a number of other, so-called clinical or laboratory methods used in general medicine, and it has the advantage of giving results, which can be expressed numerically for comparison, and which, if they indicate anything, probably show the state of irritation at the peripheral end of the extra-cardiac innervation. But for want of a better method of examination I have adopted this one, with all its reservations. In all cases of mania which I have investigated, the peripheral innervation, as denoted by this method, has been found diminished, the diminution being most pronounced with regard to the parasympathetic innervation, so that the

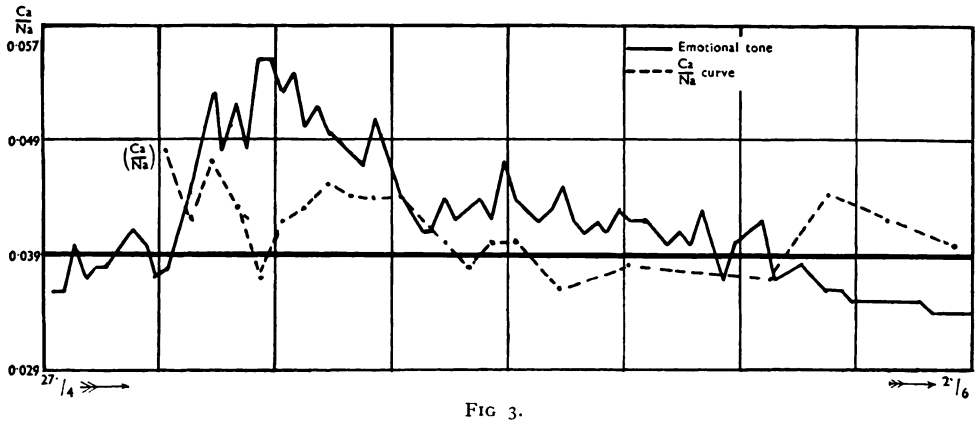

FIG 3.

sympathetic innervation has been relatively dominant. This is in accordance with the works of a number of other authors, who have characterized manic states as "sympatheticotonic". *Relatively* this is the case so far as the cardio-vascular innervation is concerned, although absolutely they are hypo-

TABLE I.—*Examples of Results of Atropine Method of Danielopolu and Carniol in Mania.*

	Patient's age.	Pulse before test.	"Sympathetic" pulse.	Inhibitory effect of parasympathetic.	Remarks. Sympathetic.	Remarks. Parasympathetic.
1	32	86	112	26	Normal	Hypo-
2	29	70	104	34	Hypo-	,,
3	32	72	98	26	,,	,,
4	54	80	88	8	,,	,,
5*	54	86	98	12	,,	,,
6*	54	68	95	27	,,	,,
7	38	68	92	24	,,	,,
8†	52	84	120	36	Normal	,,
9	24	84	90	6	Hypo-	,,
10‡	24	78	126	46	Normal	Normal
11§	64	62	112	50	,,	,,

* Diminishing mania. † Hypomania.
‡ After acetylcholine-ephedrine. § Interval.

sympatheticotonic, if one might use that word, as well as hypo-parasympatheticotonic. (I do not here concern myself with the results in depressed patients, which are somewhat different, although on the whole with the same tendency (Table I).)

Comparison of the Ca/Na ratio in serum, and the numbers for the autonomic innervation as shown by the Danielopolu test, show that there is an inverse relation between these two, i.e., to the higher Ca/Na ratio lower values for the autonomic innervation seem to correspond. If the test is significant of the peripheral irritability of the extracardiac nerves, then these inverse relations are in accordance with general physiological laws, that the Ca/Na ratio regulates the irritability of muscles and nerves, Ca decreasing and sodium increasing the irritability, as shown by Loeb and various others (Table II).

TABLE II.—*Comparison of the Values for Ca/Na and the Values for the Sympathetic and Parasympathetic Innervation.*

Parasympathetic inhibitory effect.	Ca/Na.	"Sympathetic" pulse.	Ca/Na.
13	0·047	70	0·050
14	0·045	88	0·047
18	0·050	92	0·043
30	0·043	104	0·041
38	0·043	112	0·039
40	0·041	120	0·043
44	0·041	120	0·041
47	0·040	122	0·044
48	0·037	126	0·037
50	0·039	145	0·040
53*	0·043	160*	0·034

* A patient with Graves's disease.

I may here add, that in an unpublished series of investigations on the galvanic irritability, Larsen of Brejninge in Denmark, in about 20 manic-depressive cases, found normal or greatly diminished irritability of the median nerve, and in no case an increased irritability.

These alterations in calcium and sodium in serum found in manic patients are the very opposite of those found in tetany. The same seems to be the case as regards the nervous irritability; this is increased in tetany, decreased in mania. Since 1909 an increase in Ca by giving Ca-salts has been known to decrease the irritability, and this fact has been extensively used in theoretical discussions and therapeutic attempts in tetany, etc., although they have had but little lasting success.

It seemed to me that, in a similar way to what had been done in tetany, one might eventually use the deviations in Ca and Na found in manic-depressive

patients as a starting-point for therapeutic attempts. I first tried a number of such substances which theoretically should diminish Ca or increase Na. But all of these had either no effect at all on the patients, or only a very short one. I therefore looked for substances primarily increasing the diminished autonomic innervation, and also correcting the electrolytes. After a number of attempts, ephedrine (or ephetonin) was selected to increase the diminished sympathetic innervation, and acetylcholine to increase the diminished parasympathetic innervation.

The diminution in the parasympathetic innervation being most pronounced and seemingly a more primary disturbance than the sympathetic, the main missing substance seemed to be the acetylcholine. This had not been given to patients until 1926, so that it was a relatively new substance when I began my investigations on it in 1929. By these I have been able to show that intramuscular injections of acetylcholine (1–3 mgrm. per kilo body-weight) result, as a rule, in a fall of the serum calcium and an increase of the serum sodium concentration, these changes beginning about 3–5 minutes after the injection, reaching a maximum in 15–30 minutes, and gradually again reaching the initial values in about 4 hours (Table III).

TABLE III.—*The Effect of Acetylcholine on Ca and Na in Serum.*

Name.	Date.	Dose (mg./kg.).	Before injection (mg. %.).	Minutes after injection. 5 (mg. %).	30 (mg. %).	60 (mg. %).	120 (mg. %).	240 (mg. %).
G. J—	4.x	3	Ca 12·6	..	11·6	..	..	..
			Na 250	..	320	..	..	..
			Ca/Na 0·057	..	0·041	..	..	..
	7.x	3	Ca 11·8	..	11·4	..	..	..
			Na 270	..	365	..	..	..
			Ca/Na 0·049	..	0·033	..	..	..
	8.x	3	Ca 11·6	..	11·4	..	..	..
			Na 320	..	400	..	..	..
			Ca/Na 0·038	..	0·032	..	..	..
	11.x	3	Ca 11·0	..	10·9	..	..	..
			Na 262	..	352	..	..	..
			Ca/Na 0·046	..	0·035	..	..	..
	26.x	2	Ca 11·7	11·2	11·0	10·8	..	..
			Na 320	289	312	308	..	..
			Ca/Na 0·041	0·043	0·039	0·039	..	..
	2.xi	2	Ca 12·0	11·4	11·8	11·1	11·6	12·2
			Na 282	286	292	297	312	307
			Ca/Na 0·048	0·044	0·045	0·042	0·041	0·044

i. e. Acetylcholine lowers serum calcium, increases serum sodium, and lowers the ratio of irritability, Ca/Na. The alterations in the electrolytes seem to begin within a few minutes of the injection, returning again to the original values within about 4 hours.

I am very well aware that a number of investigators, especially of recent years, are of the opinion that acetylcholine has practically no effect, or at least only a momentary one, when given to human beings. I seriously doubt, however, whether the injections have really been given *lege artis* by the authors themselves with due respect to the chemical properties of the substance, as, for

instance, the very rapid decomposition of it in solution. I never have been able to convince myself of the stability of any solution of acetylcholine. I have had ample opportunity to control the relative lack of effect of acetylcholine, for instance when given by a less conscientious nurse or some of the younger assistant colleagues. It is absolutely necessary that the powder should not be dissolved in water until you are at the bedside, and then the injection must be given at once, intramuscularly and not subcutaneously.

In a number of psychotic cases I have interrupted the treatment with acetylcholine and given physiological solution of sodium chloride in equal amounts. The effect has been very different—absolutely none with the NaCl, as against an evident "sedative" action of the acetylcholine. In a number of cases with cerebral thrombosis or embolism I have used acetylcholine during the last four years. The invalidity of these cases compared with former cases shows a very striking difference, the former cases remaining invalids in about 50%, the acetylcholine-treated ones in about 10%.

My opinion of the effectiveness of acetylcholine administration has been strengthened by these results, despite the opinions of some other esteemed colleagues. I have also tried doryl, a more stable choline preparation, still more potent than acetylcholine. But the effect on the blood-electrolytes does not seem to last more than half an hour or so. The fall in serum calcium may be severe, and I have seen a patient getting something like a tetanic fit after doryl injections.

Whereas acetylcholine has to be given by intramuscular injections, ephedrine may be given by mouth, and only in relatively small doses, as the sympathetic innervation is as a rule less diminished than the parasympathetic.

Both ephedrine and acetylcholine, besides influencing the autonomic system, seem to diminish serum calcium and increase serum sodium, and should thus *a priori* correct both the nervous and the humoral changes found in manic patients.

So far the dosage of the substances has been individually varied, according to the total impression which the patients have presented from day to day.

Ephedrine has been given first in doses of a quarter to half a tablet of 5 cgrm. ($\frac{1}{6}$ gr.), to ascertain the tolerance, and then, according to the severity of the case, increasing to 3–5 tablets a day given perorally. In extreme cases it can be injected subcutaneously.

Acetylcholine has also been varied daily, according to the state of the patients, 10–20 cgrm. (2–3 gr.), one to six times per day, according to the severity of the case. The preparations have been obtained from Lematte & Boinot, in Paris, and Hoffmann-Laroche in Basle.

The results of my experiments with these substances have been that at the same time as the diminished innervation was increased and the changes in the blood-electrolytes corrected, the psychotic phase of the patients blew off in a considerably shorter time than otherwise would have been expected.

At first I had each patient isolated and kept under permanent supervision and gave all the injections myself. No other drugs, baths or mechanical restraint was used. Only patients who had had previous attacks of mania or melancholia and were known to have recovered were at this time accepted for the treatment, and only cases of pure phasic mania, without atypical, schizophrenic or hysterical symptoms. Thirteen patients were treated under these conditions. The average total duration of their former attacks was 144 days (varying between 60 and 330); the average total duration of the attack treated with acetylcholine and ephedrine was 43 days, and of these, 23 came before the beginning of the treatment; the treatment itself lasted 6·3 (2–16) days; the convalescent time was 14 (or 6–25) days (Table IV).

TABLE IV.—*Cases of Mania, privately treated, during* 1930–1932, *with Acetylcholine-Ephedrine. Duration of Manic Attack.*

Name.	Sex.	Age.	Duration (in days). Before treatment.	Of treatment.	Of convalescence.	Total duration.	Duration of earlier attacks.
1. S. K. E—	M.	18	6	7	18	31	90
2. S. E—	F.	32	12	6	10	28	150
3. R. D—	F.	60	4	7	20	31	90
4. G. M—	F.	66	15	3	5	23	90–180
5. I. G—	F.	26	8	10	6	24	122
6. H. S—	F.	20	12	2	8	22	122
7. T. G—	M.	25	60	4	12	76	122
8. T. A—	F.	36	30	6	21	57	240–300
9. E. G—	M.	36	10	3	9	22	210–330
10. I. K—	F.	56	92	16	15	123	240
11. A. K—	F.	60	21	3	13	37	150
12. I. O—	F.	50	14	10	21	45	150–220
13. F. T—	M.	54	14	5	25	44	60–90
Average			23	6·3	14	43	144

In other words, in these 13 cases privately treated with acetylcholine and ephedrine, the total duration of the manic attack was only a quarter that of previous attacks. Although all of them were severe cases, the possibility could not be excluded that they would all have recovered in the same short time without these medicaments, as other conditions were also somewhat extraordinary (isolation, supervision).

To check these preliminary results and try to find out the role of the medicaments in the treatment, all except four patients with mania admitted to the New State Mental Hospital in Reykjavik during 1933–35 have been treated with these drugs. To eliminate the possible beneficial effect of the isolation, all the patients have been treated in wards of 18–24 patients without isolation. No manual or mechanical restraint has been used, and they have not been given more attention by the staff than any others in the ward. These patients, after they have received the injections, become more wakeful.

They soon quieten down, and in a few days sleep is restored to relatively normal. The appetite is good, as well as other somatic functions. The face soon becomes pale, through the effect of the ephedrine; if this pallor seems to be excessive the dose of ephedrine is diminished, which also is done if the patients complain of palpitation. I have seen no other inconveniences from the treatment. The injections have been given by the house physicians, or in some cases by the nurses, the number of injections to be given being fixed by me during the visit in the morning. The patients have, as a rule, not received other drugs, but in a few cases for experimental reasons another drug may have been given once or a few times, and four or five times in all hyoscine has been given by an inexperienced house physician, as a precautionary measure. Without exception my impression is that whatever hypnotic or sedative has been given, the after-effect is not good, and seems to counteract the acetylcholine and ephedrine. The conditions under which the patients have been kept must be considered as exciting as possible for these patients, who were all known to be extraordinarily sensitive to external disturbances. Hence these conditions should probably help to make the results as pessimistic as possible, or at least avoid making them too bright. In the same direction it also had the effect that, acetylcholine being relatively expensive and our means limited, we have always tried to diminish the dose as soon as possible, and therefore often too soon, so that it had to be increased again. It also has happened that we have had difficulty in procuring the drug, which, of course, has prejudiced the results.

Of the total of 310 admissions during these years, 29 cases have been mania, i.e., the frequency of mania in proportion to the total admissions is as 1 : 10·7. Of these 29 cases, 4 were not treated remedially at all, for the sake of control (Table V).

TABLE V.—*Cases of Mania in the New Mental Hospital at Reykjavik not treated Remedially.*

Name.	Sex.	Age.	Duration (in days). Before treatment.	Of treatment.	Of convalescence.	Total duration.
1. J. H—	M.	33	197	77	120	406
2. S. J—	M.	29	45	87	10	142
3. M. J—	F.	70	180	200	15	395
4. T. B. G—	M.	50	96	37	52	185
Average			129	100	49	282

These patients have, on the average, stayed 149 days in the hospital.

Twenty-one cases of phasic mania have been treated with acetylcholine and ephedrine according to the lines which I have mentioned. The average

duration of their stay in hospital is 61 days, and of these the treatment itself has lasted 33 days (Table VI).

TABLE VI.—*Cases of Mania treated in the New Mental Hospital at Reykjavik during* 1933–1935, *with Acetylcholine-Ephedrine.*

Name.	Sex.	Age.	Duration (in days). Before treatment.	Of treatment.	Of convalescence.	Total duration.	Duration of treatment and convalescence in earlier attacks.
1. J. M. T—	F.	21	150	14 (14)*	136	300	400–500
2. S. E—	F.	20	16	12 (12)	13	39	30–60
3. O. F—	F.	27	141	32 (20)	43	216	..
4. A. T—	F.	17	8	7 (6)	9	23	..
5. O. A. J—	M.	15	31	38 (20)	14	83	..
6. J. J—	M.	53	6	23 (12)	9	38	30, 365, 365
7. H. J—	M.	43	7	29 (26)	16	52	331
8. G. T—	M.	24	62	75 (17–42)†	4	141	90–180
9. B. J—	M.	47	14	12 (6)	69	95	..
10. J. M—	M.	78	14	17 (17)	25	56	9–100
11. M. B—	M.	31	11	31 (31)	68	110	..
12. G. H. S—	M.	15	3	19 (17)	11	33	..
13. O. F. E—	M.	16	3	13 (13)	4	20	..
14. O. G—	M.	40	14	17 (17)	12	43	..
15. H. T—	M.	43	6	55 (29)	12	73	..
16. M. M—	F.	30	108	21 (14)	7	136	140
17. K. T—	F.	67	183	44 (6)	10	237	..
18. G. O. S—	F.	14	88	69 (13)	8	185	..
19. G. T—	M.	26	30	125 (25)‡	9	164	90–180
20. G. H—	M.	54	44	34 (29)	72	150	80–300
21. V. E. T—	M.	56	30	10 (7)	30	70	..
Average			46	33 (18)	28	108	

* The numbers in brackets indicate on how many days injections of acetylcholine were given. In some cases the ephedrine treatment was continued longer than the acetylcholine.

† After 17 days the acetylcholine was out of stock for a month. Then it was resumed, and given for 25 days.

‡ For experimental reasons doryl was first tried during 100 days. No effect.

In 8 of these cases the duration of earlier attacks is known, and averages 174 days.

The total duration of the acetylcholine and ephedrine-treated attacks of these patients has been 95 days, 46 of which have elapsed before the patients were admitted to the hospital. The duration of the convalescence was 35 days, and of the actual treatment therefore only 14 days.

If the results of this Table VII are compared with the average numbers of

TABLE VII.—*Duration of Manic Attack treated in Hospital with Acetylcholine-Ephedrine. A Summary of* 8 *cases where the Duration of Earlier Attacks is known.*

Duration (in days). Before treatment.	Of treatment.	Of convalescence.	Total duration.	Duration of treatment and convalescence in earlier attacks.
46	14	35	95	174

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TABLE VIII.—*Comparison of Private and Hospital Patients treated with Acetylcholine-Ephedrine.*

	Duration (in days).			Total duration.	Duration of treatment and convalescence in earlier attacks.
	Before treatment.	Of treatment.	Of convalescence.		
13 private patients	23	6·3	14	43	144
8 hospital patients	46	14	35	95	174

Table IV, as done in Table VIII, it is evident that the conditions in the case of the hospital patients have not been so good as in the case of the privately-treated patients, and especially has the time of convalescence been longer with the hospital patients. The duration of the convalescence depends on many things which the hospital cannot control, but must be taken into account in order to avoid misunderstanding, as the only criterion of recovery which cannot very well be doubted by others, is the definite discharge from the hospital into outside life. Nevertheless the results in both these groups compare favourably with the duration of earlier attacks in the same patients, but which were treated in a different way.

The effect on the final results of variations in the duration of the psychosis before admission may be seen from Table IX.

TABLE IX.—*Comparison of Cases of more than 4 Months' Duration before Admission.*

	Duration (in days).			Total duration.
	Before treatment.	Of treatment.	Of convalescence.	
4 cases treated with acetylcholine-ephedrine	143	28 (17)	49	222
4 cases not treated with acetylcholine-ephedrine	129	100	49	282

It will be seen from the Table, that this does not seem to affect the duration of the acetylcholine-ephedrine treatment, which, in these cases, was 28 days, as against 100 when these substances were not used.

Table X shows a comparison of the duration of cases admitted during the first month of the disease, and those admitted after 4 months.

There is no difference in the time required for treatment or convalescence.

Therefore, institution of this treatment as early as possible is the main thing which can be done to shorten the total duration of the attack of mania.

TABLE X.—*Comparison of Cases Admitted during the First Month of the Illness and those Admitted after 4 Months, both treated with Acetylcholine-Ephedrine.*

	Duration (in days).			Total duration.
	Before treatment.	Of treatment.	Of convalescence.	
Admitted during the first month . .	23 .	31 .	23 .	77
Admitted after 4 months	143 .	28 .	49 .	222

Besides these cases of typical, phasic manic attacks, I have had the opportunity of trying the treatment also in 4 cases of acute exacerbations in constitutional hypomaniacs. I have applied the treatment intermittently. The total duration of the exacerbations in these cases has been about 261 days. Whether the treatment is of any use in such cases, more than to quieten down the patients when they are most excited, I would not like to say, as definite criteria for the estimation of results are wanting in these cases (Table XI).

TABLE XI.—*Average Duration of 4 Cases of Manic-Depressive Constitution in a Manic Phase.*

Duration (in days).			Total duration.
Before treatment.	Of treatment.	Of convalescence.	
78 .	148 .	30 .	261

Three of the patients have been readmitted to the hospital within three years, two with acute mania, which was treated in a similar way and with comparable results, and one with a severe melancholia, which terminated in suicide.

Summarizing our results of the treatment of phasic cases of mania in the New State Mental Hospital in Reykjavik, the average stay in the hospital of these patients was 61 days, or 2 months, when the patients were treated with acetylcholine and ephedrine.

It might be inferred that perhaps our cases of mania in Iceland were different from those in other countries with European population, or that we diagnosed mania too often. This last argument is not very probable, as the incidence of mania in proportion to the total admissions is much the same in the two mental hospitals in Reykjavik (1 : 12 in the Old, and 1 : 10·7 in the New).

As already pointed out, cases in our hospital not treated with acetylcholine and ephedrine lasted up to 9 months, and those admitted after 4 months lasted 7 months. In cases where the duration of former attacks is known this seems to have been 5–7 months. All this suggests that the types of mania that we have are not different from those in other countries. This

receives additional support through the fact that of 425 admissions to the Old Mental Hospital, where acetylcholine and ephedrine had not been used, 33 were mania. Of these, 3 have died, 2 are still in the hospital. The remaining 28 show an average stay in the hospital for the whole group of 11 months, for 24 phasic cases of 6 months, and for 4 constitutional cases $3\frac{1}{2}$ years (Table XII).

TABLE XII.—*Duration of Stay in Hospital of 70 Cases of Mania under Consideration.*

	Treated with acetyl-choline-ephedrine.	Treated with hypnotics.	Not treated remedially.
Privately treated (13 phasic cases)	39 days	..	..
Treated in hospital (21 phasic cases)	61 ,,	180 days (24 cases)	149 days (4 cases)
Treated in hospital (4 constitutional cases)	178 ,,	1268 days (4 cases)	..

These, together with my own cases, show that the cases of phasic mania occurring in Iceland are probably not different from those in other countries with white populations. Therefore on the average our patients with mania stayed 6 months in hospital before the beginning of the acetylcholine and ephedrine treatment. After the adoption of this the patients on the average have stayed 2 months in the hospital, or a third of the previous time.

If this result is the consequence of the treatment itself, it may show the value and possibilities of the biochemical and neuro-physiological approach towards manic-depressive psychosis, or at least to some forms of it. In the further investigation of these, I submit that the acetylcholine and ephedrine-treatment might be a step of some value, and at least worthy of further investigations by better qualified men, and under better conditions than I have had.

SUMMARY.

The treatment of manic attacks by acetylcholine and ephedrine seems to me to be superior to other forms of treatment, but it must be conducted conscientiously, regularly and individually according to the case.

In any case it can be maintained (1) the treatment is not dangerous, (2) it does not prolong the attacks, (3) it rather seems to shorten them, probably to one-third of the usual time, if begun early in the phase.

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