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METHODS IN EVALUATING THE THERAPY WITH L-DOPA IN PARKINSON'S SYNDROME

by

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1. Introduction

The effect of anticholinergic substances on rigor, tremor, akinesia an other symptoms of Parkinson's syndrome has been known for over 100 years . FELDBERG (1) postulated (1945) as Central acetylcholine–atropin antagonism and proved 1948 that the highest concentration of acetylcholine can be found in the striatum. The application of acetylcholine to the pallidum during stereotactic operations intensifies the tremor of the contralateral extremities (NASHOID (1959) (2).

Biochemical analysis of the basal ganglia showed that not only acetylcholine but also the catechlamines dopamine and noradrenaline, as well as serotonine have a transmitter function. At first, indifferent brain regions characteristic differences in the concentration of the biogenic amines were found. In normal persons dopamine is highest concentrated in the striatum, noradrenaline in the region of the hypothalamus, from where it diminishes caudal. This is comparable to the concentration of serotonine in this region,

which however, increases caudal (subst. nigra, base of 4th ventricle) EHRINGER and HORNYKIEWICZ (3) 1958. In Parkinson–patients the concentration of dopamine in the striatum and the concentration of noradrenaline in the hypothalamus are lower than in normal persons (4). The concentration of serotonine is also decreased and shows a normal distribution only in the region of the formatio reticularis.

The idea to connect the relative concentration of biogenic amines to the functions of certain brain strutures is obvious. The correlations are still uncertain, since too little is known about the functions of the mentioned amines in the brain.

Our present knowledge of biochemical disorders in Parkinson's syndrome are based on the chemical analysis of the brain- parenchyma of untreated and treated patients suffering from Parkinson's disease, clinical observations after substitution-trials and examinations to the amino acid spectra of the cerebro-spinal fluid .

L-Dopa, L-3, 4-dihydroxyphenylalanine, is the immediate precursor of dopamine and is able to pass the brain-barrier-systems after intravenous or parenteral application .The decarboxilation to dopamine is probably done by a nonspecific L-amino acid-decarboxylase, sufficiently active in patients suffering from Parkinson's syndrome and sufficient ly active during treatment with L-Dopa. Probably the biochemical defect could be found in a decreased activity of tyrosinhydroxylase,which is known to catalyse the rate-limiting step of dopamine synthesis .

A first indication for the connection between structural defects and biochemical changes in Parkinson's syndrome could be found in the disappearance of the melanine- containing cells of the nucleus niger and its connection to the dopam ine-deprived stri atum (.5,6, 11).Further indications arise from our findings that the tyrosine content in CSF increases after i. v. injection of L-Dopa (7,8) and after long-term treatment with L-Dopa(9).The transient automatic and effective disorders in Parkinson's syndrome are explained by BIRK-MAYER

(1972) (10) as a disturbance of the release of serotonine and noradrenaline respectively .The mentioned disorders may be treated with L-5-hydroxytryptophane or L-tryptophane .

During the last few years, extensive analysis of amino acids in the cerebro- spinal fluid in healthy persons and patients suffering from Parkinson's disease and other extrapyramidal disorders were made. (9,12) Preliminary results permit prognosis of a favourable effect of therapy with L-Dopa in Parkinson's syndrome, if characteristical changes of the amino acid composition occur (9) .

In short , the following statements can be made with some certainty regarding the biochemistry of parkinson's syndrome :

1. Decrease of the content of the catecholamines dopamine and serotonine in certain regions of the brain of patient's with Pakrinson's syndrome, also in cases with intact cell structure (3, 13,)
2. Decreased excretion of dopamine-metabolites in the urine (14)
3. Alleviation of the Parkinson's symptoms, including tremor after application of L-Dopa, the immediate precursor of dopamine (15,16).
4. Transient influence of monoamino oxydase inhibitors on the Parkinson-symptomatology (17, 18).
5. Exacerbation of the Parkinson-symptomatology after the application of reserpine or phenothiazines caused by releasing biogenic ami es (19, 20,) or blocking dopaminergic receptor respectively.
6. Application of L-5-hydroxy tryptophane and L-tryptophane may avoid temperature regulation disorders, a transient symptome of Parkinson's disease (2.1, 2.2).
7. The amino acid composition in CFS is disturbed characteristically in Parkinsonism -e.g. the content of glycine and serine is elevated it is normalised after application of L-Dopa (12,).

II. Cases And Techniques Of Examination

The following report includes 37 patients suffering from Parkinson's disease who were treated with the L–Dopa preparate Levopa * (capsules of 500 mg each).

The group consisted of males and 17 females. The average age was 56,5 years, the youngest patient was 48 years, the oldest 70 years. Most patients were suffering from paralysis agitans (31 patients) while in 4 patients a postencephalitic Parkinsonism was assumed. Two other patients showed symptoms of arteriosclerosis cerebri besides paralysis agitans. 20 patients at the Neuro–Psychiatric Clinic of the University of Vienna, Austria, 10 patients were treated at the Neuro–Psychiatric Clinic, Medical School of Bagdad, Iraq and 7 at the Department of Neurology of the Szpital Miejski Katowice, Poland. The time of observation ranged between 6 weeks and 18 months.

The severity of the disease was classified into four grades according to the "patient neurological and disability rating scale" . More than half of the patients (20) had severity grade III, 8 patients severity grade IV, 7 patients severity grade II and 2 patients severity grade I. In order to estimate the effectiveness of the L– Dopa treatment, the tremor was separately classified into three severity grade. Seven patients were without tremor, 16 patients with a slight, 11 patients with a medium severe and 3 patients with asevere to very severe tremor.

The treatment was initiated in 14 cases while the patients were still in hospital,the rest were treated as out-patients.Fifteen patients had no anti-parkinson therapy before, 2 of them showed severity grade I,7patients severity grade II and 6 patients severity grade III . All other patients had already received conservative anti-parkinson drugs (14 patients), or other L-Dopa preparates (8 patients), 6 of whom showed severity grade Iv and 3 severity grade III.

*We have to thank ICN, Pharmaceutics Inc., Irvine, California, USA for relinquishing the test quantity.

Before treatment all patients were examined physically,where by special attention was given to the heart and the circulatory system as well as to the digestive system. Patients with severe cardiac damages , severe hypotension and those with increased signs of arteriosclerosis were excluded from the L-Dopa therapy. Cases with signs of arteriosclerosis were examined by EEG and those who showed an abnormal EEG were also excluded, as well as patients with symptoms of kidney disorders.

A few cases were given no medication 5 days prior to the treatment with Levopa . Medium severe and severe cases were left without medication until the symptoms of parkinsonism became apparent. The 9 mentioned patients with a previous L-Dopa therapy are listed in a separate table(table la) . None of the patients who were initiated with or changed to Levopa were given amantadine immediately before the beginning of the therapy.

Treatment was undertaken with an initial 500 mg dose 1 capsule, with a stepwise increase of 500 mg within 4 to 5 days until the necessary dosie was reached.The average dosis was 2,84 g /day in all 37 patients including those 9 who already had previously another L-Dopa preparation. The highest dosis was 5g / day (2 patients), the lowest dosis 1g / day (1 patient with severity grade I). From the reported results, mediun to asevere cases always required a 2-3g daily dosis.

Seven patients with a marked tremor of severity grade III received a combination of L-Dopa with Cogentin with a daily dosis between 3×1/2[to 3×1 tablet . Four further patients whose therapeutic results were judged satisfactory to unsuccessful were given a combination with Aturban . Three of these cases showed some improvement of rigidity an akinesia after having received 3×1 tablet of the mentioned drug. These 4 cases were not given special consideration for the combination-effect with conservative drug . Aturban was given only after the study was completed.

The course of the therapy and the therapeutic results were judged from several points of view.

1. All patients had a thorough physical examination and were controlled at regular intervals(initially every3days, after2weeks once weekly,

after 6 weeks at intervals of 3 to 4 weeks. Theseinvestigations included a neurological and psychiatric examination as well as a questionaire on side effects.

2. In 25 of the cases the clinical data were scored according to WEBSTER ratim g scale, besides clinical examinations and controls.
3. ubjective evaluation of the therapeutic results by the patient was made with the aid of standardized questionaires, i.e. a self rating scale, as well as drawing and writing tests in 25 cases.
4. In 51 cases a standardized set of tests of a psychodiagnostic test battery (PDT) was used, testing the finemotoric functions , the associative mobility, alertness the amnestic functions and the speed and mobility of the motoric course. Using these tests, conclusions on the changes of rigidity, akinesia and tremor are possible (GERSTENBRAND et al, 1873) (23)
5. The amino acids in CSF were controlled in 1 1 cases.
6. Finally rigid examinations of the side effects were carried through and laboratory tests were made for side effects on liver, kidney and blood picture with systematic controls at fixed intervals (see chapter Iv) .

111 . RESULTS AND DOCUMENTAION

1. Regular physical examinations:

The results of the treatment of Parkinson,s syndrome with L — Dopa are summarized in table 1 . As seen , in only three cases unsuccessful therapy was observed . Two of the cases had severity grade Iv, one severity grade II . In 18 patients the effect 8 Parkinson symptoms were, good in 9 patients excellent and in 7 cases the clinical effect was satisfactory . Between the severity grade of the disease and the therapeutic results no definite correlation could be made .

2. WEBSTER rating scale :

Using WEBSTE R rating scale to judge the efficacy of the therapy (see table 2) a significant improvement could be observed on the patients in items 2 , 7 and 10 controlled 35 times ; which stand for rigidity , ammia

and akinesia and independency . Item 4 , swinging along of the arms , of WEBSTER rating scale shows in 5 cases an exacerbation , a condition which does not fit into the general pattern . No marked changes are found in items 3 , 5 , 8 , 9 (posture , walk , seborrhea and language) . It should be considered however, that most patients (21)did not have any disturbances of the mentioned items (3, 5, 8, 9) at the begin of this study .

3. Self rating scale and writing test :

From the self—rating scale,which was answered regularly by 24 patients, no item showed an aggrevation except of the general well — being the aggrevation for the general bieng in four cases was connected with the side effects which appeared during treatment . A depressive state was not looked upon as a side effect and was treated with Dibenzepin . Generally it can be said that the value of the self— rating scale. It is far too dependent on the daily state , misunderstandings and suggestion of the members of the family .

The writing and drawing tests made by 27 of patients showed in 12 cases a clear, in 15 a slight and in 7 cases no improvement. It is noticeable that especially the drawing tests showed a clear improvement, whereas the improvement of the writing and drawing tests paralleled the clinical amelioration of the general state.

It is difficult to evaluate a long lasting L-Dopa therapy in relation to tremor, therefore this category of symptoms has been referred to separately.

The particular category of symptoms concerning tremor was evaluated separately, due to the difficulty of an evaluation of a long lasting therapy with L-Dopa.

In nearly half of the patients, as seen in table 3, L-Dopa was not able to produce an effect on tremor. Twelve patients showed a definite and 4 patients a slight improvement .No correlation between the grade of severity of tremor and the effectiveness of the therapy could be found. Only in cases with severe tremor the improvement was more marked. It is to note, that severe tremor is not basically connected with the severity of Parkinson's disease.

4. Psychodiagnostic test battery (PDT)- see table 4, 14 patients were tested as described below.The clinical severity grade was II to III.The mean age of this patients was 53 years, with a standard deviation of 16, 99. The high standard deviation is cause by two particulary young patients (21 19 years).

Everyone of the examined patients had preliminary a test to learn. The second test was performed approximately 3 weeks after reaching the optimal dosees of the drug.

The statistical evaluation of the tests was done by calculating the mean value, the standard deviation and the significance by means of the t-test for associated random samples. All tests showed a significant (at least 5%) improvement during treatment as compared to controlls. The significance was considerable in the "number symbol test"as well as in the test for the examination of fine motoric at the one percent level. The same result was found in the reproductability of numbers.

The test battery consists of :

a) Motoric function test according to GRUNBERGER: A standardised chart with 100 areas in ten rows is used . The patient has to set as many points as possible into the bordered off areas , first by the right and then by the left hand. Number andexactness of placement of the points is rated. The psychomotoric coordination and the sensomotoric abilities are assessed by this test.

Indications on the patient's impulses may be gained, particulary the severity of tremor,which is judged by the placement of the points .(24)

b) Number symbolic test according to OTIS: The problem of this test is to associate a number of symbols one another . Conclusions may be drawn from this test on associative mobility as well as visual ability of learning and remembering . Especially in Parkinson's syndroms akinesia and the emotional alertness may be evaluated . (25)

c) "Crossing out test" according to GRUNBERGER :
Forty-seven prescribed letters must be crossed out as fast as possible'

first by right then by left ,the time needed for each side is evaluated separately .The course of mobility ,of swiftness of mobility and of flexability is tested. Herewith in Parkinsonism conclusions on tremor, akinesis ,rigor respectively can be made . (23)

d) "Crossing out test" according to BRICKENKAMP (d 2-test) :
Attentiveness, stressability and ability of concentration are tested. The number of letters crossed out and the number of error are rated after transposition into standard grades .(26)

e) The "alphabetic cross-out test" according to GRUNBERGER :
The patient has to cross out the letters A,N,E,X from a row of ordered letters within a time limit of 10 seconds per row. The dedicated attentiveness and the ability of concentration are tested. (27)

f) Memory test according to KOHIMANN and ARNOLD :
The patient has to repeate 10 two-digit numbers by head . Answers allow to make conclusions on some brainfunctions and the afficiency of the brain (23)

In conclusion it can be said that the results of the psychological and subjective impressions give abetter method for quantifying therapeutic results than do clinical rating scales.They transmit the improvement during the therapy with L- Dopa much better than does the course grou Ping into severity grades of grades of the disease or classification of the various symptoms into severity grades . The self rating test cannot classify sufficiently the subjective impression of the patient because no aggravation was admitted by them .

5' Examination of the free amino acids in CSF :
previous papers reported that about 70 % of 72 tested potients suffering fromparalysis agitans showed in the cerebrospinal fluid a characteristisc change of the pattern of the amino acids :

The concentration of glutamic acid was lowwer than in control (controls: ×−90 mg % patients×0= , 12 mg %) . The concentrations of glycine(0,32 resp.0,60)serine(0,36 resp.0,57) cysteine+cystine(0 , 19

resp.0 74), threonine(121 resp.0,44) and methionine(0,07 resp. 0 , 18 however , were higher . During th treatment with L Dopa clinical improvement paralleled the normalisation of the amino acid spec - trum

L- Dopa treatment was ineffective in patients with a normal concentration of the amino acids prior to the treatment ,(9)

Cerebro - spinal fluid and venous blood were examined both samples were taken at the same time . The tested patients are described in table 5 .

a) 4 ml of CSF were acidified of pH 2 , desalted by column chromatography (6×0 , 4 cm, cation exchange resin Dowex 50 × 4 H+ Form ph 2) .
After washings with 4 ml 0, 01 N HCL and 6 ml H_20,5 ml2 N NH_3 were used as eluant . The eluate was eva porated (to dryness) and dissolved with 250 ml 0 , 05 N HCL. Aliquots were taken for anaysis (Amino - Acid - Analyser TSM l , F a . TechnlKon , franKurt main)

b) lml of blood serum was deprotinized with trichlor - acetic acid (10%) centrifuged 15 min . at 3000 g . The precipitate was washed washing and the first supernatant were combined acidified to pH 2 and traeted as described in a)

These findings are verified on a serie of other patients.

a) Patients (case No. 1-4) with very good therapeutic results (table 6):
Out of the 19 analysed amion acids,serine, glycine,tyrosine and phenylalanine are emphasized in the table. In the 4 probands a decrease in concentrations of serine and glycine could be demonstrated in the spinal fluid, while the amount of tyrosine and / or phenylalanine increased (patient 1 and 2) or remained uneffected (patient3 and 4). Changes of the amino acids of the serum were not proportional to those measured in the spinal fluid.

b) Patients (case No. 5-8) with satisfactory therapeutic results (table7)
In this group of patients the amino acid spectrum was similar to those of group a . It is to be noticed, that in case no. 7 at beginning of the treatment, the spinal fluid contained approximately100mg album in,

a condition which may have resulted from a change of the capillar permeability. For this reason, in spite of successful treatment,the concentrations of serine and glycine were increased in the spinal fluid as well as in the serum. One and a half months later, the concentration of the proteins in CSF was considerably lower and at the same time the concentrations of serine and glycine were as low as we expected.

c) Patients (case No. 9-11) with unsuccessful therapy-results (table8):
Patients 9-11 showed a completely different picture of the amino acids in CSF.The concentrations of serine and glycine were nearly unaltered in case no. 9 and 10, in case no. 11 they were increased even more without respective change in the serum. Tyrosine and phenylalanine also remained practically unaltered.

It is worth while mentioning that in all probands the concentration of glutamic acid in CSF was maximally 0,23 mg%,which is below the normal concentration of healthy persons (approx. 1 mg%) . In case no. 5 (table7)this concentration was normalized. The concentration of all other amino acids stayed within the biological deviation during the time of observation.

The present observations confirm former reports (9,12) about a correlation between a successful L-Dopa therapy and a special disorder in the anion acid pattern of CSF of the untreated patients. These results support our assumption that there are least two types of paralysis agitans with various disturbances of the brain metabolism but without clinical differences. No correlation was found with respect to severness and duration of the disease and changes of amino acid composition of the cerebro spinal fluid.

IV. SIDE EFFECTS

Besides various physical complaints, especially of the digestive system mental disturbance may arise duringa long-term therapy with L-Dopa.(29)

Twelve patients of the 37 tested cases in this study were suffering from somatic side effects. Initially there were 8 cases with nausea, 4 with vomiting. In one patient the L-Dopa therapy had to be discontinued because

of persistant vomiting. In four of the seven remaining cases these side effects could be controlled by deminishing the daily dosis while the other three cases were successfully treated with mild antiemetica.

Side effects on the heart and circulatory system were very rare. Only four patients showed low blood pressure with subjective complaints of dizziness and tiredness. In one patient of this group the low blood pressure was only transitory, the other three were treated with antihypotonica . One of these cases showed a short-lasting disturbance of the cardiac rhythm requiring no treatment.

Psychiatric complications were apparent in 5 of the patients. Three patients had a depressive transitory-syndrome. One patient showed a clear enhancement of moodiness. The depression could be brought under control within 1 to 2 weeks with Dibenyepin. The euphoria subsided without treatment after 12 days. Only one patient developed a state of confusion during the night, four days after the effective dosis of th edrug was reached.

This particular case was a 69 year old woman who also showed signs of arteriosclerosis cerebri. Only in two cases all together the therapy had to be interrupted because of side effects.

In conclusion, the side effects of the digestive and circulatory systems appeared mainly at the beginning of the therapy. However, it was not necessary to change the plan of therapy because of them. More serious side effects such as the psychic disturbances appeared only after the optimal dosis was reached. In these cases it was sometimes possible-by reducing the dosis to bring the disturbances to a minimum or at least reduce them to a bearable state.

YAHR, already in 1968 (30) called attention to an incipient hyperkinesis after a certain period of treatment, which caused a considerable influence on a continous excellent effect of treatment of the long-term L-Dopa therapy. Although most American authors had given a much higher daily dosis. Of the 37 cases analysed here, 7 showed hyperkinesi isnvolving the muscles of the face and the tongue in all cases.

Five patients also showed involvement of the distal extremities, three of whom a marked hyperkinesis of both big toes, in two cases on the right side only. Four patients of this group were not troubled enough by the restlessness making a decrease of the daily dosis unnecessary. In the remaining three patients, by reducing the dosis by 500 mg, the hyperkinesis was alleviated to such an extent that no considerable interference with the continuation of the treatment through this side effect existed. A connection between dosis and appearance of hyperkinesis could not be made. However, all 7 patients with the above mentioned side-effect were a moderate to medium severe case of parkinson's syndrome.

V. SUMMARY

A report about 37 patient suffering from a moderate to medium sever parkinsonism of different etiology is given. The patients were treated with L-Dopa preparate Levopa Two-thirds of the cases satisfactory to very satisfactory therapeutic results, three cases had no improvement of the general state. The therapy had to be interrupted in two cases because of side effects the side effects in ten other cases stayed within bearable limits .

Evaluation of the efficacy of the therapy in the long run is best done by a combination of psychomotoric examinations (PDT) self-rating tests and neurological tests, rather than using standard rating scales alone. Also in 11 cases analysis of the amino acid composition in CSF was performed, the results were in good correlation with the results of other tests .

TABLE 1

Total Therapy Results And Severity Grade

	I	II	III	IV	Total
No improvement	0	1	0	2	3
Slight improvement	0	2	4	1	7
Well	1	1	12	4	18
Excellent	1	4	3	1	9
Total	2	8	19	8	37

I – IV *Severity grade*
0 – 3 *Results of therapy*

TABLE 2

Results of Webster - Rating Scale

Items	–	0	+	Total
I	0	15	20	35
II	1	10	24	35x
III	1	19	15	35
IV	5	13	17	35
V	0	18	17	35
VI	0	17	18	35
VII	3	12	20	35x
VIII	1	31	3	35
IX	1	27	7	35
X	0	7	28	35x

X = Significant at the 5 % level

TABLE 3

Effect on Tremor

	I	II	III	Total
0	9	2	2	13
1	4	5	3	12
2	2	0	2	4
3	0	0	0	0
Total	15	7	7	29

I–III severity grade of the tremor independent of other symptoms of Parkinson's disease
0 – 1 - 2-3 *therapy results*

TABLE 4

Comparison between examination 1 and 2 as well as values of normal persons .

1. Examination		x	s	2 Examination	x	s	t-test	normal values
a) motoric right standard value		81, 7	9, 3		84, 2	8, 6	3, 2 1 %	100 SW
motoric left standardvalue		83, 9	8, 6		95, 2	8, 3	2, 3 5 %	100 SW
right+left standard vaule		81, 9	9, 3		84, 8	8, 1	3, 8 1 %	100 SW
b) digit symbol		5, 5	2, 3		7, 9	0, 8	2, 8 5 %	7, 54 AM
c) cross-out test in seconds,								
	right	38, 1	15		32	14	1, 89 n.s.	18 sec.
	cross-out est in second,left	49, 2	26		40, 2	16, 6	2, 5 5 %	21 sec.
d) d 2-test total number,								
	stand. value	84, 8	6, 6		85, 6	6, 9	2, 3 5 %	100 SW
	d 2-test total number minus mistakes standard vaule	83, 0	8, 0		84, 0	8, 2	2, 25 5 %	100 SW
	d2- test basic val . of mistakes	24, 3	12, 9		23, 3	8, 8	0, 79 n.s.	50 %
e)	AD test total val.	84, 5	7, 5		86, 7	9, 5	5, 2 5 %	100 SW
	AD test total val. minus mistakes	83, 0	8, 0		82, 5	8, 8	2, 1 5 %	100 SW
	AD test basic val. of mistakes	26, 0	15, 1		21, 9	14, 4	1, 72 n.s.	50 %
f) memory for digits		3, 07	1, 32		4, 07	0, 91	4, 7 1 %	5–7

x = mean value S = standard deviation SW = standard value

n.s = not significant AM = mean value of age

TABLE 5

Patients taken into the study with Parkinson syndrome

No.	Pat.	age	duration of disease	complaints A	complaints R	complaints T	therapy results	side effects
1	K. S.	49	3	++	++	+	+++	none
2	R. J.	62	8	+++	++	+	+++	angionoidal complaints
3	G. G.	64	4	++	++	+	+++	none
4	P. M.	72	6	++	++	+	+++	slight dizziness and nausea
5	S. A.	50	7	+	++	+++	++	chills
6	G. K.	55	5	+	++	++	++	none
7	K. M.	58	2	++	++	–	++	none
8	S. M.	62	4	++	++	+	++	none
9	D. K.	60	6	+	+	++	+	dizziness, psych.astasia
10	G. H.	70	10	++	++	–	+	circulatory disorders
11	B. G. ♂	59	3	+	+	++	–	———

TABLE 6

Change of concentration of some amino acids in the cerebro-spinal fluid and in blood-serum in patients with very good therapeutic results.

Pat. No.	Dose of Levopa		Percentile change of concentrat on duration of treatment .			
			CSF	serum	CSF	serum
			22 d		11 Mo	
1	2 g/day	Ser	0	- 12	- 40	- 10
		Gly	0	0	- 60	- 10
		Tyr	+ 300	0	+ 350	- 30
		Phe	+ 40	- 30	+ 50	- 65
			11 d		31/ 2Mo	
2	2 g/day	Gly	- 10	-	- 35	-
		Tyr	+ 20	-	+ 120	-
		Phe	0	-	+ 85	-
					3 Mo	
3	2 g/day	Ser			- 55	- 30
		Gly			- 30	- 15
		Tyr			- 15	0
		Phe			- 20	0
			38 d			
4	2 g/day	Ser	- 80	- 40		
		Gly	- 50	- 30		
		Tyr	0	0		
		phe	0	0		

TABLE 7

Change of concentration of some amino acids in the cerebro-spinal fluid and in blood-serum in patients with satisfactory success of therapy

Pat. No.	Dose of Levopa		Percentile change of concentration Duration of therapy			
			CSF	serum	CSF	serum
			15 d			
5	2 g/day	Ser	0	+ 40		
		Gly	0	30		
		Tyr	+ 50	+ 25		
		Phe	+ 40	0		
			35 d		4 Mo	
6	2.5g/day	Ser	- 40	- 40	- 40	0
		Gly	- 20	0	- 20	+ 35
		Tyr	+ 100	+ 65	+ 75	+ 75
		Phe	+ 90	- 25	+ 90	+ 40
			14 d		11/ 2 Mo	
7	1.5 g/day	Ser	+ 30	+ 80	- 30	0
		Gly	+ 30	+ 115	0	- 30
		Tyr	+ 50	+ 90	+ 50	- 30
		Phe	+ 65	+ 100	+ 65	0
					7 Mo	
8	3.5 g/day	Ser			- 80	- 45
		Gly			- 80	- 35
		Tyr			+ 40	+ 170
		Phe			+ 250	+ 200

TABLE 8

Change of concentration of some amino acids in the cerebro-spinal fluid and in blood -serum in patients with moderate success of therapy.

Pat. No .	Dose of Levopa		Percentile change of concentration Duration of treatment			
			CSF	serum	CSF	serum
			14 d			
9	?	Ser	-20	0		
		Gly	0	0		
		Tyr	0	-20		
		Phe	0	0		
			21 d		2 Mo	
10	2 g/day	Ser	-20	-	-	-
		Gly	0	-	0	-
		Tyr	-25	-	-50	-
		Phe	0	-	0	-
			52 d		7 1/ 2Mo	
11	2-3 g/day	Ser	+ 160	- 20	0	-40
		Gly	+ 55	- 20	0	-20
		Tyr	+ 130	+ 75	0	+ 70
		Phe	0	+ 30	0	+ 45

LITERATURE

1 . FELDBERG, W., present views on the mode of action of actylcholine in the central nervous system. physiol.Rev.25 (1945) 596-642

2 . NASHOLD,B.S., Cholinergic stimulation of globus pallidus in man. Proc. Soc. exp. Biol. Med. N.Y. 101 (1959) 68-69

3 . EHRINGER,H., und HORNYKIEWICZ,0., Verteilung von Noradrenalin und Dopamin (3-hydroxytyramin) im Gehirn des Menschen und ihr Verhalten bei Erkrankungen des extrapyramidalen Systems. Klin. Wschr. 38 : 1236, 1960

4 . BARBEAU,A., Les catecholamines dans la maladie de parkinson Proc. 7th Intern. Neurol . Congr . Roma Societa Grafica Romana 2:925, 1961

5 . HORNYKIEWICZ,0., Die topische Lokalisation und das Verhalten von Noradrenalin und Dopamin (3-hydroxytyramin) in der Substanzia nigra des normalen und parkinson-Kranken Menschen. Wien. klin. Wschr. 75,309-312 (1963)

6 . POIRIER,L.J.,et T.L.SOURKES,Influence of the substantia nigra on the catecholamine content of the striatum.Brain,88,181-192(1965)

7 . BRUCK,H.,F. GERSTENBRAND, E. GRUNDIG,R. TEUFELMA-YR , Uber Ergebnisse von Liquoranalysen beim Parkinson syndrom. Acta neuropath. (Berl.) 3, 638-644, 1964

8 . GRUNDIG,E.,F . GERSTENBRAND,H . BRUCK,P . PROSENZ, H.GNAD,R.TEUFLMAYR und I. BINDER, Der EinfluB von Aminosauren, speziell von L-Dopa und Alpha-Methyldopa auf au die Zusammensetzung des Liquor cerebrospinalis bei extrapyramidalen Syndromen. Veranderungen d r Liquorzusammensetzun g nac h L-Dopagaben bei parkinsonpatienten und Gesunden. Dtsch.Z. Nervenheilk. 196,236 (1969)

9 . GRUNDIG,E.,F. GERSTENBRAND, J. OBERHUMMER,M. SIMANYI,R. SCHEDL, J. WEISS, Biochemische Aspekte der L-Dopa-Wirkung bei Parkinsonpaticnten.z . Neurol. 203, 73-90, 1972

10. BIRKMAYER,W., Der derzeitige Stand der Therapie mit L-Dopa. Medical Tribune, internationale Wochenzeitshrift fur Deutschland 5(18B):5
11. CARLSSON,A., the occurrence, distribution and physiological role of catecholamines in the nervous system, pharmacol. Rev. 11 (1959) 490-493
12. GRUNDIG,E.,F. GERSTENBRAND, Uber den Zusammenhang zwischen der Parkinsonsymptomatik und einer Storung des Aminosaurehaushaltes im ZNS. Wien. klin. Wschr. 82, 811-816, 1970
13. BERNHEIMER,H., BIRKMAYER,W. and HORNYKIEWICZ,O., Verteilung des 5-hydroxytryptamins (Serotonin) im Gehirn des Menschen und sein Verhalten bei Patienten mit Parkinson -Syndrom. Klin. Wschr. 39: 1056, 1961
14. HARE,T.,A.,BEASLY,B.CHAMBERS,R.and VOGEL.Plasma and urinary levels of Dopa and other amino acids in L-Dopa treated patients with Parkinsons disease .Federation Proceedings,29:952, 1970 .
15. BIRKMAYER W. and HORNYKILWICZ,O., Der L-3, 4-doxythenylalanin (Dopa)- Effekt bei der Parkinson Akinese. Wien. Klin Wschr. 73: 787, 1961
16. GERSTENBAND, F., PATEISKY, K.,uber die Wirkung von L-Dopa auf die motorischen Storungen beim Parkinson-Syndrom. Wien . Z. Nervenheilk . 1962, 20,90
17. BARTHOLINI, G., PLETSCHER, A., Effect of various decarboxylase inhibitors on the cerbral metabolism of dihydroxyhenylalanine. Journal of Pharmacy and Pharmacology, 21: 323-324, 1969
18. BIRKMAYER, W., Experimentelle Ergebnisse uber die Kombinationsbehandlun des Parkinson-Syndroms mit L-Dopa und d einem Decarboxylasehemmer (Ro 4-4602). Wien .Klin Wschr. 81: 677,1969
19. COLE, J.O., and D. J. CLYDE, Extrapyramidal side effects and clinical response to the phefothiazines. Rev. canad. Biol. 20, 565-574 (1961)

20. UHRBAAND, L. and A. FAURBYE, Reversible and irreversdyskinesia after treatment with perphenazine, chlorpromazine, reserible pine and electroconvulsive therapy. Psychoparmacologia 1 (1960) 408-418
21. MARGHERITA,G., Il comportamento della resistenza elettrica cutanea nelle sindromi parkinsoniane. Acta neurol. Napoli 19, 698-709 (1964)
22. PENNES, H.H., Temperatures of skelet l muskle in cerebral hemiplegia and paralysis agitans .Arch, Neurol. Psychiatr. Chicago 62 269-279 (1949)
Quantitative
Langzeittherapie beim parkinson- Syndrom .Nervenarzt 44, 428-433 (1973)
24. GRUNBERGER,J., Klinisch-psychologische Teststudie an Alkoholkranken (Test zur prufung der Motorik) In.K. Kryspin-Exner:Die offene Bruder Hollinek 1967
25. WECHSLER,D., Die Messung der Intellingenz Erwachsener (Zahlensymboltest) Bern : H. Huber 1956
26. BRICKENKAMP,R . Aufmerksamkeitsbelastungtest , Tes t d-2, Gottingen: Hogrefe 1962
27. GRUNBERGER, ., Untersuchung der Konzentration und Aufmerksamkeit , In: K. Kryspin-Exner, die offene Anstalt fur Alkoholkranke in Wien Kalksburg, S.65-67, Wien : Bruder Hollinek, 1967
28. ARNOLD,O.H . , KOHLMANN,TH. : De r Zahlengedachtnistest Wien Nervenheilk. 4, 1-8 (1952)
29. COTZIAS,G.C . , PAPAVASILIOU,P.S . an dGEELLENE,R.., Modification of parkinsonism: CChroni ctreatment with L-Dopa. New Engl. J. Med .280: 337, 1969
30. YAHR,M.D., and DUVOISIN,R.C., Medical therapy of parkinsonism . Mod. Treatm.5: 283, 1968