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Treatment of multiple sclerosis and paralysis agitans with tolbutamide 1-butyl-2-p-tolysulfonylurea

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THE TREATMENT OF MULTIPLE SCLEROSIS AND PARALYSIS AGITANS
WITH TOLBUTAMIDE 1-BUTYL-3-P-TOLYSULFONYLUREA

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The Treatment of Multiple Sclerosis and Paralysis

Agitans with Tolbutamide

1-Butyl-3-p-Tolylsulfonyleurea

Recently three articles have appeared regarding the use of tolbutamide, which is a drug widely used in the treatment of mild diabetes mellitus, in diseases other than diabetes mellitus; namely in Pustular Acne (1), in Multiple Sclerosis (2), and in Paralysis Agitans(3). In each series presented, the patients treated seemed to respond remarkably well with striking remissions of symptoms of the particular syndrome under study.

In 1953 Loury, Moore, and Coilliet (4) published a paper which discussed the treatment of multiple sclerosis with Adenosine-5-Monophosphate , after which the author noted rather subtle improvements in bladder disability and overall physical endurance. This was associated with high pyruvic acid levels in the serum of multiple sclerosis patients.

They agreed with Jones, Jones and Bunch (5) that multiple sclerosis may be a metabolic defect in carbohydrate metabolism with a block somewhere in the pyruvic acid-lactic acid level.

Henneman, Altschule, Gonez, and Alexander (6) in studying the metabolism of carbohydrate in multiple sclerosis found that the elevated levels of pyruvic acid reported by Loury, Moore and Coilliet (4) were actually elevated levels of alpha keto glutaric acid and postulated a defect in the handling of the small carbohydrate fragments in multiple sclerosis.

With this in mind, it was decided to enter upon a double blind study utilizing patients with multiple sclerosis and paralysis agitans.

Material

Six patients with multiple sclerosis and six patients with paralysis agitans were located through the facilities of the University of Nebraska Hospital, University of Nebraska Clinics and the Douglas County Annex. A drug company provided

us with identical tablets labeled 60-P and 61-P-the one drug being tolbutamide and the other being a placebo. One patient was maintained on tolbutamide for the entire period of this study. Artane and Benadryl were used in two cases of paralysis agitans. The diets were the standard hospital diets which consisted of 240 grams of carbohydrate, 90 grams of fat, and 84 grams of protein. In some cases this was altered to consist of 195 grams of carbohydrate with no limit to the amount of fat or protein. In one case a patient was placed on a controlled diet consisting of 195 grams of carbohydrate, 65 grams of fat and 86 grams of protein.

Method

The patients were divided into two groups (tables 1&3) consisting of multiple sclerosis patients and paralysis agitans patients. Base line neurological examinations were then done on each patient, and oral glucose tolerance tests were done where feasible. Regimens of treatment were started as

shown in (tables 2 & 8). The patients were maintained on these regimens for periods of from 7 to 54 days as shown in (tables 9 & 10). No quantitative measurements were used in this study. All evaluations were done by means of neurological examinations and are recorded using a modification of the clinical grading system of Loury and Associates (4), and shown in (tables 9 & 10).

Results in Multiple Sclerosis

In evaluating patients with a disease such as multiple sclerosis, which is characterized by many remissions and exacerbations, it is difficult to determine if the remission or exacerbation is due to treatment with some particular drug, or just the natural course of the disease. One important observation noted in these patients was the eager manner in which they grasped at this opportunity to find a treatment that may help them.

In this small group no striking changes were seen to

take place either with 60-P or 61-P, tolbutamide or diet.

There were some subtle changes noted which seemed to be related to the therapy. These seemed to be related mostly to deep tendon reflex activity and sensory alterations. Case 1 is of interest because this patient seems to have had a rather marked improvement in his gait, EEG findings, and in his ability to organize and solve spacial problems. The greatest improvement seemed to occur with Number II and III diets (table 4). In the other patients any improvement noted seemed to be related to 60-P, but all the changes were slight.

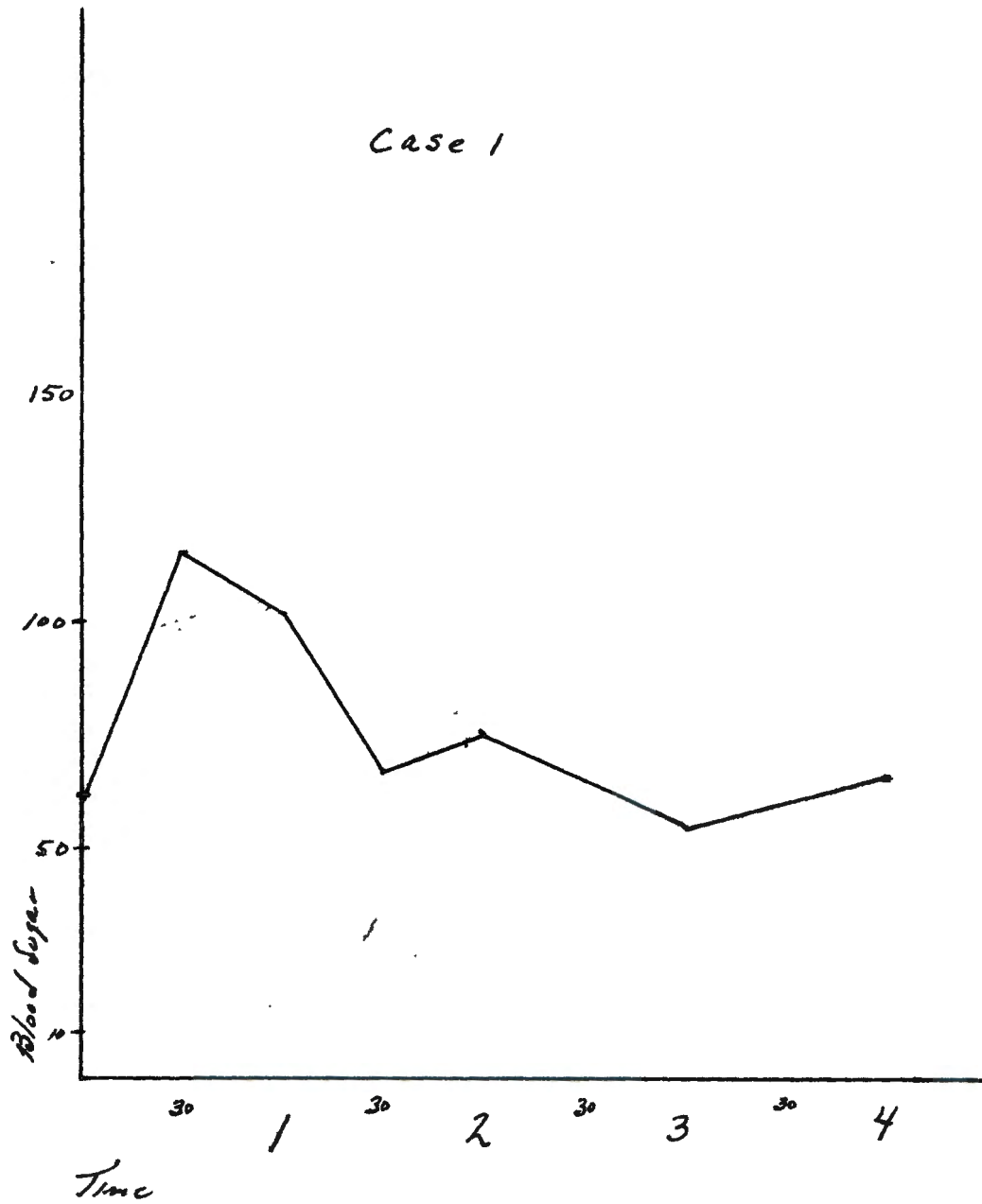
Results in Paralysis Agitans

In evaluation of results in cases of paralysis agitans, we looked for changes in tremors, rigidity, posture and ease of movement. In this series of patients no marked difference was noted in the patient's response to either 60-P or 61-P. In cases 2 and 4 the response seemed to be related to 60-P. Case 2 had difficulty with hypoglycemic reactions on three

occasions. The response in case 4 was most marked when the patient was on Artane and Benadryl. Case 6 responded to 61-P. In all cases the response was a decrease in tremor and in case 2, an alteration in rigidity was noted.

Multiple Sclerosis Cases (Tables 2 & 9)

Case 1 A 28 year old white male whose illness has lasted 11 years and has been characterized by many remissions and exacerbations. This patient was first seen on November 3, 1960, at the University of Nebraska Hospital. His chief complaint at this time was excessive salivation and difficulty in walking. When examined the patient was found to have a severe spastic ataxic gait. The Romberg Test was positive. Coordination was reduced, dysdiadochokinesia was more marked in the right forearm. Motor strength in the patient's upper extremities was good and symmetrical. Motor power in his lower extremities was reduced. His right leg was weaker than the left leg.



Glucose Tolerance Test

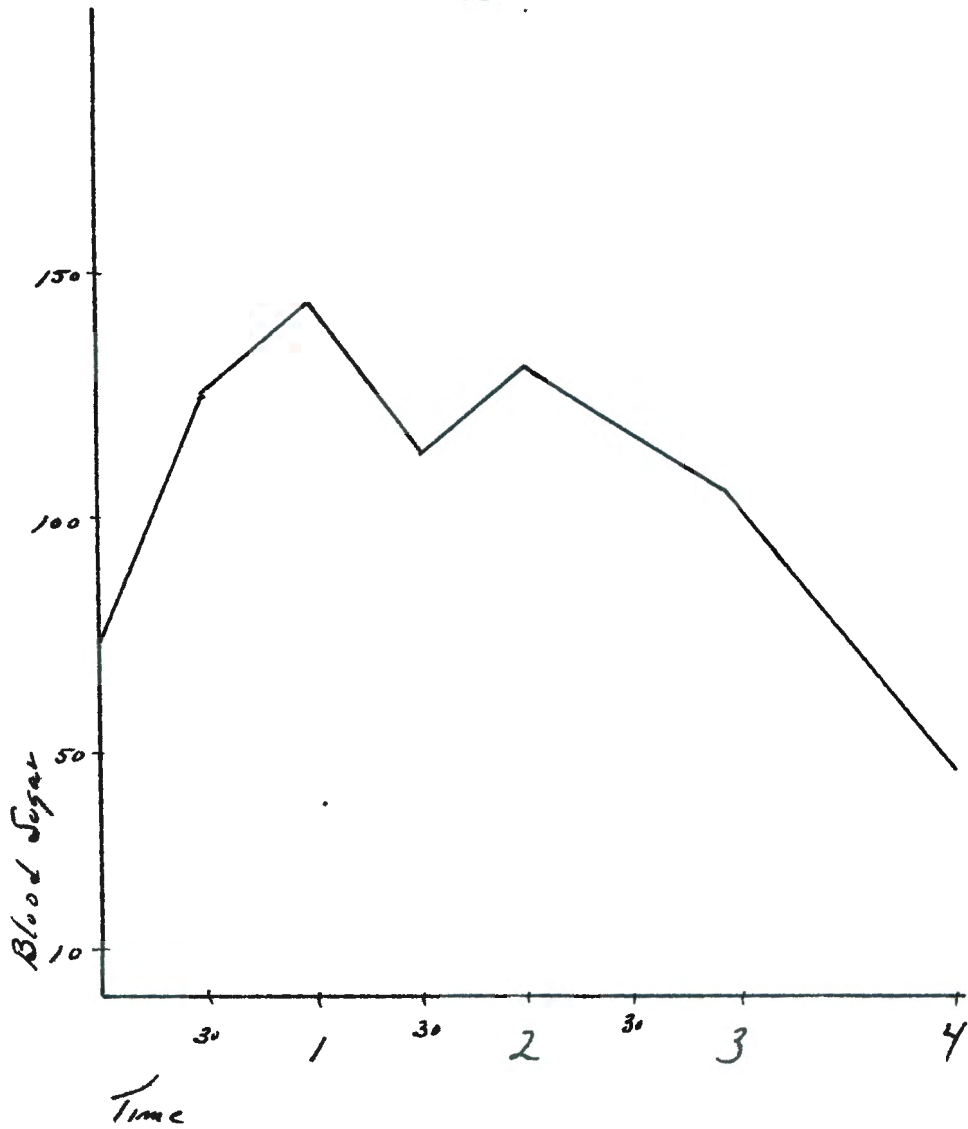
Table 5

The deep tendon reflexes in the upper extremities were asymmetrical being almost absent in the right upper extremities. He had bilateral hyperactive lower extremity reflexes., sustained ankle clonus bilaterally, and position sense was reduced in the lower extremities. Vibratory sense was diminished from the hips and was absent in ankles. An oral glucose tolerance test was done (table 5) prior to starting him on 500 mgms of tolbutamide twice a day, and on physical therapy. After 11 days the patient was re-examined and there was no remarkable change from the previous examination . The patient was then started on Diet No. II (table 4) with 500 mgms of tolbutamide twice a day. He was examined in seven days, and at this time there were some changes noticed. The patient's balance had improved slightly, his reflexes were symmetrical in the upper extremities, and vibratory sense in the ankles had improved. After 18 days the patient's gait had improved. A psychological evaluation at this time revealed a dramatic

change in the patient's intellectual functioning, especially in the ability to organize and solve visual spacial problems. An electro-encephalogram done at this time showed a change from abnormal focal slow activity in the right temporal area, to a minimal diffuse slow activity. The tolbutamide was stopped, and the patient was placed on a regular diet and after 25 days a deterioration in his gait, equilibrium and deep tendon reflexes was noted. Tolbutamide was started again of 2 grams a day and a regular diet was given. In 20 days a rather marked improvement in equilibrium was noted with improved gait and reflexes. The patient noticed a marked decrease in salivation. He was then switched to a special diet (table 4) and examined in 14 days when further improvement in gait, balance and coordination was noted.

Case 2 This patient is a 56 year old white male who has had multiple sclerosis since 16 years of age. This illness was characterized by remissions and exacerbations with

Case 2



Glucose Tolerance Test

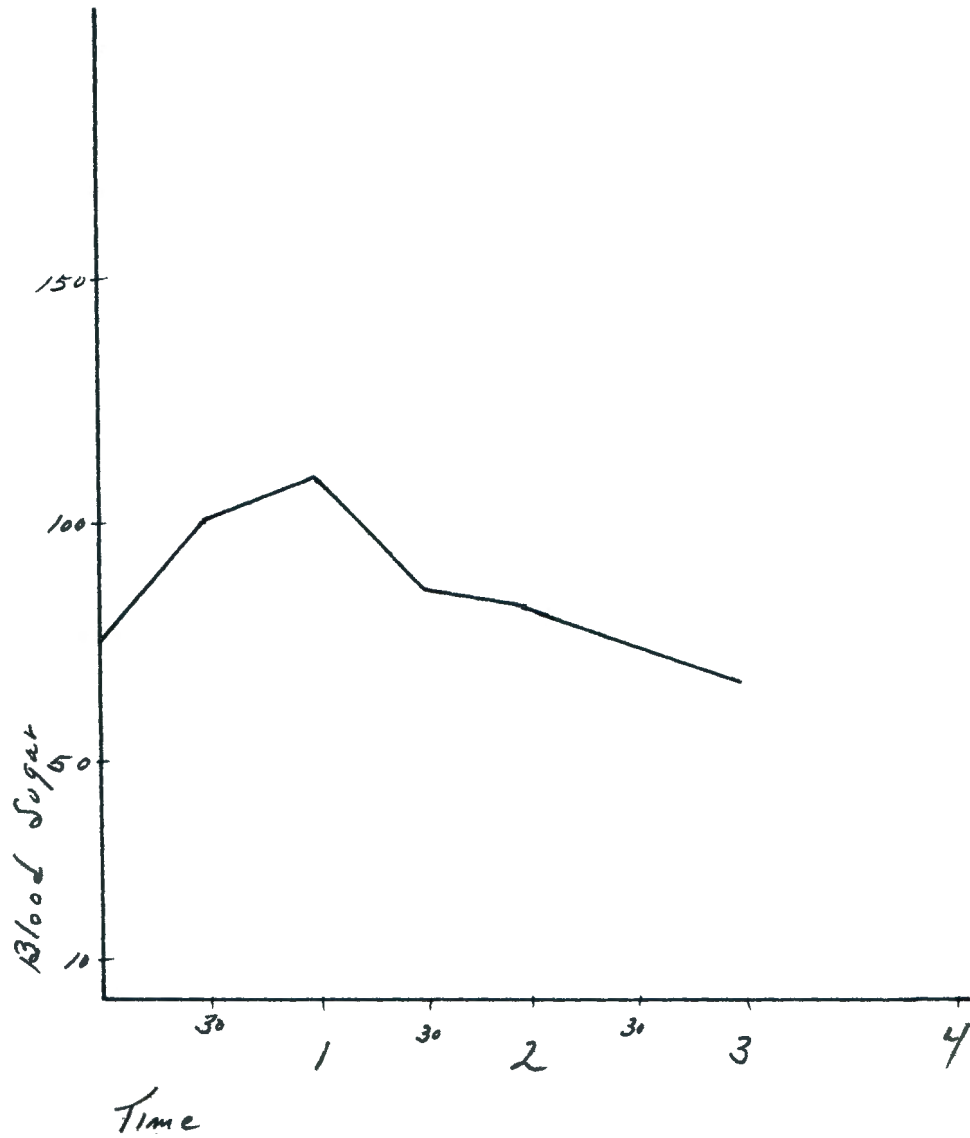
Table 6

progressive weakness, and at the present time the patient uses a wheel chair. This patient was followed as an out patient and was first seen on November 10, 1960. He was able to walk with the aid of a cane. He had a scissors type gait, narrow base, ataxic, and spastic coordination. His balance was poor, and motor power was good in the upper extremities. There was marked weakness from the waist down and inability to lift the right leg while sitting, although he could raise the left leg. The deep tendon reflexes of the upper extremities were hyperactive, abdominal reflexes were absent. Lower extremity reflexes were hyperactive with sustained ankle clonus. Babinski and Chaddock signs were present bilaterally. A positive Hoffman was noted on the left hand. Position and vibration sense were reduced symmetrically below the knees. He also had difficulty controlling his urine. The patient was enthusiastic to the point of being euphoric. An oral glucose tolerance test was done (table 6) and the patient

started on tolbutamide, 1 gram per day. After 15 days the patient was re-examined and there was essentially no change. He was then started on 61-P and seen in 20 days. This time the patient came down the hall without his wheel chair. He was happy. He still had a spastic ataxic gait with heavy dependence on his cane. He was changed to 60-P and re-examined in 23 days when further improvement was noted in gait and some improvement in balance and more control of the bladder. The patient was switched to 2 grams of 60-P a day and he was seen in 7 days. The gait was improved somewhat and bladder control was better.

Case 3 This patient is a 54 year old white male whose illness has been present for 27 years and has been characterized by remissions and exacerbations. This patient was seen on an out patient basis. He was first examined on November 14, 1960, and found to have bilateral temporal pallor of the discs, reduced peripheral vision and dysarthria. He used a wheel

Case 3



Glucose Tolerance Test

Table 7

chair at times and he also used crutches. Coordination in his upper extremities were reduced and his speech was slow and slurred. Motor power of the upper extremities was good, and the motor power in the lower extremities was markedly reduced especially on the right. The reflexes were minimal to absent in both upper and lower extremities. Position sense and vibratory sense was absent from the hips down. An oral glucose tolerance test was done (table 7) and the patient was started on 60-P, 1 gram a day, and re-examined in 20 days. A change in position and vibratory sense was noted and good reflexes were obtained bilaterally. The patient was then placed on 61-P, 1 gram a day, and re-examined in 25 days at which time reflexes were very difficult to obtain and the vibratory sense had again diminished. The patient was now placed on 61-P, 2 grams a day, and re-examined in 7 days. His examination at this time is essentially unchanged from his previous examination. After 14 days it seemed more difficult to obtain reflexes and the patient seemed

to be generally the same as when he was first examined.

Case 4 The patient is a 42 year old white male whose illness has been present for 25 years and characterized by remissions and exacerbations. He was followed at the Douglas County Hospital Annex. He was first examined on December 20, 1960, and found to spend most of the day in a wheel chair. He was able to transfer from the chair to bed and was receiving physical therapy at that time. His right arm was paralyzed; he could move the right shoulder. His left arm was weak but he could dress himself and button his shirt. He could not move his legs. Reflexes were asymmetrical with hyperactivity in right upper extremities, with sustained right wrist clonus and bilateral ankle and patellar clonus. The patient was placed on 1 gram of 60-P per day and on Diet No. II (table 4). He was re-examined in six days and was found to have reduced reflexes in the upper extremities. The patient was then started on 61-P, 1 gram a day, and re-examined in 27 days

when reflexes in the upper extremities were asymmetrical being almost absent on the left. Clonus was sustained in the right wrist and of short duration in the ankle. Position sense was reduced and vibration was absent in the ankles and reduced from the hips down.

Case 5 A 49 year old white male who first had symptoms of multiple sclerosis in 1940 and whose disease had progressed so that by 1955 the patient was unable to leave his bed being dependent for all care. He was followed at the Douglas County Annex and was first examined on December 20, 1960. At that time the patient was noted to have horizontal nystagmus. He could not move the left arm, but he could open and close the left hand with difficulty. He could move his right hand and arm, although coordination was poor. His lower extremities were paralyzed and quite spastic when stimulated. There was sustained bilateral ankle clonus and right sustained patellar clonus. He was able to get into a chair for 3/4 of an hour a day.

Table 1
Data on Patients with Multiple Sclerosis

Case No	Age at Study	Duration	Age of Onset
1	28	11	17
2	56	40	16
3	54	27	27
4	42	25	7
5	49	20	29
6	42	6	36

Table 4
Description of Diets

Diet	I	II	III
Carbohydrate in grams	240	195	195
Fat in grams	90	ad lib.	65
Protein in grams	84	ad lib.	186

Table 2
Data on Patients with Multiple Sclerosis

Case	Date	11	11	11	11	12	12	12	12	12	12	12	1	1	1	1	1	1	2	2	2	
		4	17	18	25	1	4	9	16	19	20	21	10	13	14	19	27	30	2	11	13	
		60	60	60	60	60	60	60	60	60	60	60	61	61	61	61	61	61	61	61	61	
	Diet I	x	-----					x	-----					x	-----							
1	Diet II		x	-----	x	-----																
	Orinase	x	-----										xx	-----	xx	-----						
	Diet III																		x	-----		
	Diet I		x	-----																		
2	60-P												x	-----	xx	-----						
	61-P				x	-----																
	Orinase	x	-----																			
	Diet I				x	-----																
3	60-P				x	-----																
	61-P												x	-----	xx	-----						
	Diet II															x	-----					
4	60-P															x	-----				x	-----
	61-P																		x	-----		
	Diet II															x	-----					
5	60-P																		xx	-----		
	60-P															x	-----					
6	Diet II															x	-----					
	Orinase															x	-----					

*Diets as per table 4
xx 2 grams

Babinski, Chaddock and Oppenheim signs were present bilaterally.

The patient was started on 61-P, 1 gram a day, and re-examined

in 25 days. Nystagmus was absent; he had bilateral sustained

ankle and patellar clonus. Position and vibratory sense were

absent and there was a possible increase in superficial sen-

sations. The patient's legs and feet felt warm to the patient.

He was next placed on 2 grams of 60-P a day and re-examined in

13 days. His reflexes were as they were when first examined.

He had a hypersensitivity to touch in both legs, which was

almost a burning sensation. He was able to move the right

big toe and was able to raise his left arm from the bed.

Spasticity of the lower extremities was still marked although

not as much as when first examined. Personnel working with

the patient in physical therapy thought that the patient was

improving. The patient was continued on the 60-P, 2 grams a

day, and re-examined at 14 days. Horizontal nystagmus was

noted bilaterally. He did not have sustained patellar clonus.

He had been having fewer spasms of muscles in the lower extremities.

Case 6 A 42 year old white woman who had been blind since birth and who developed multiple sclerosis at the age of 36 years, and who had had a rapid down hill course and at the present time gets around by the means of a wheel chair.

This patient was followed at the Douglas County Annex and was first seen by me on December 19, 1960. She was found to be able to transfer on and off her wheel chair and was able to care for herself. Coordination was fair to good in the upper extremities, with weakness in the upper extremities more marked on the left, and a marked symmetrical weakness of the lower extremities. Deep tendon reflexes were hyperactive symmetrically with sustained ankle clonus. Babinski, Chaddock and Hoffman signs were present bilaterally. Position sense was reduced in the lower extremities and vibratory sense was reduced from the hips down. The patient was having difficulty with her bladder control. She was given tolbutamide, 1 gram a day, and was put on Diet No. II (table 4) and re-examined in 54 days.

She was noted then to have sustained spontaneous bilateral patellar clonus and sustained ankle clonus with muscle spasms of the legs.

Paralysis Agitans (Tables 8 & 10)

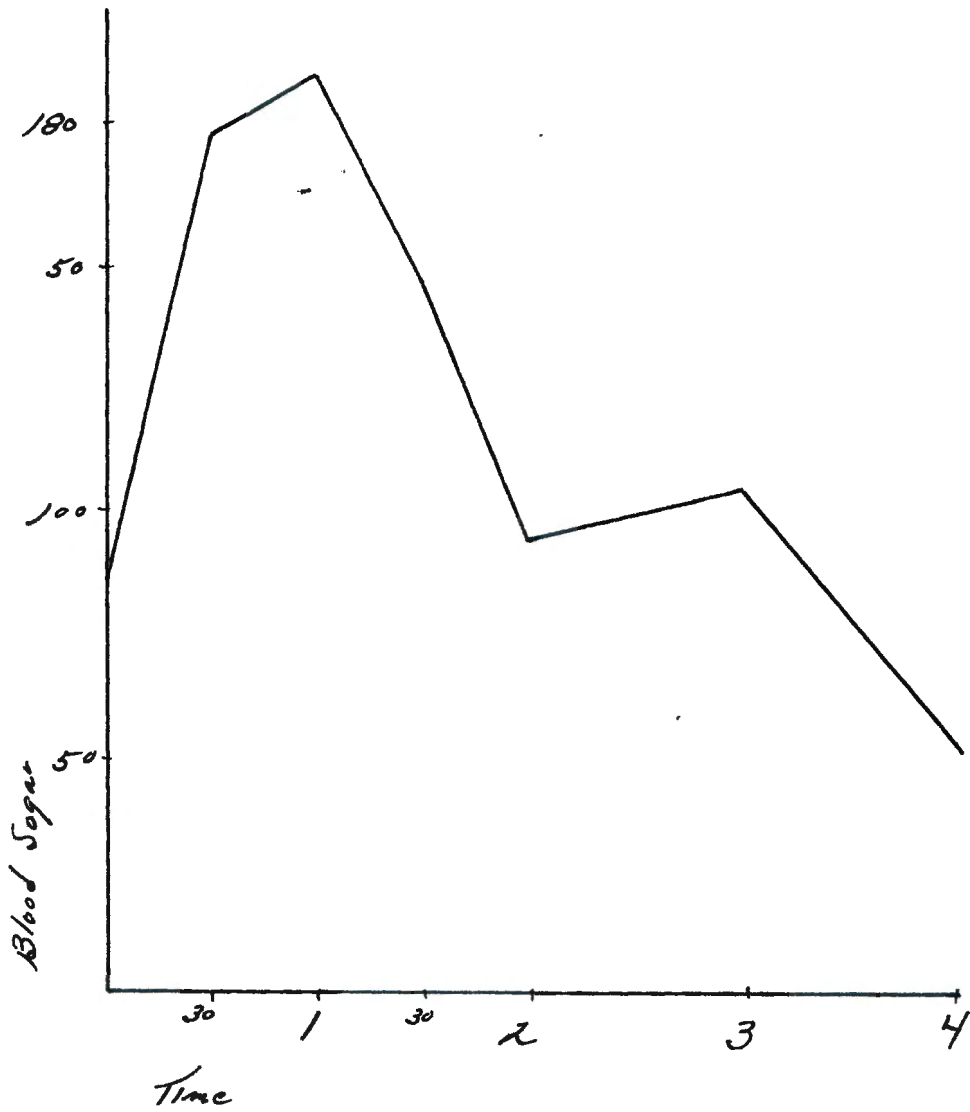
Case 1 An 86 year old negro woman who first noted a tremor 17 years ago. She was seen at the University of Nebraska Clinics in 1955 and complained of being unable to do fine needle work. She was diagnosed as having paralysis agitans. In 1958 the patient began to have a pill-rolling type of tremor and was treated with Artane and Benadryl. This patient was examined by me on November 10, 1960 when examination showed a slight ptosis of the eye lids and reduced facial motility. She walked with a short steppage gait and a minimal stoop. The patient's equilibrium was good. She had a pill-rolling tremor that was most marked in the left hand. There was a minimal cog wheel rigidity. The patient was started on 500 mgms of tolbutamide twice a day as shown in (table 8) and

Table 9
Changes in Symptoms of Multiple Sclerosis

Drug	Symptoms										
	D	D	D	C	B	C	D	A	S	S	S
1	Orinase 1 Gm	I	14	0	0	0	0	0	0	0	0
	Orinase 1 Gm	II	18	0	+	+	0	-	0	0	0
		II	7	-	0	0	+	+	+	0	0
		I	32	0	-	-	-	-	0	0	0
	Orinase 2 Gm	I	20	0	+	+	+	0	+	0	0
	Orinase 2 Gm	III	14	+	0	+	0	0	0	0	0
2	Orinase 1 Gm	I	15	0	0	0	0	-	-	0	0
	61-P 1 Gm	I	20	0	0	+	0	0	0	0	0
	60-P 1 Gm	I	25	0	+	+	0	0	0	0	+
	60-P 2 Gm	I	20	0	+	+	0	0	0	0	+
3	60-P 1 Gm	I	20	0	0	0	+	0	+	0	0
	61-P 1 Gm	I	25	0	0	0	-	0	-	0	0
	61-P 2 Gm	I	20	0	0	0	0	0	-	0	0
4	60-P 1 Gm	II	25	0	0		+	+	0	0	0
	61-P 1 Gm	II	28	0	0		-	-	0	-	0
5	60-P 2 Gm	II	28	0			+	+	+	+	0
	61-P 1 Gm	II	25	0			+	0	+	0	0
6	Orinase 1 Gm	II	54	0	0		-	0	0	-	0

* 0 - no change
 + - improvement
 - - degeneration

Case 1



Glucose Tolerance Test

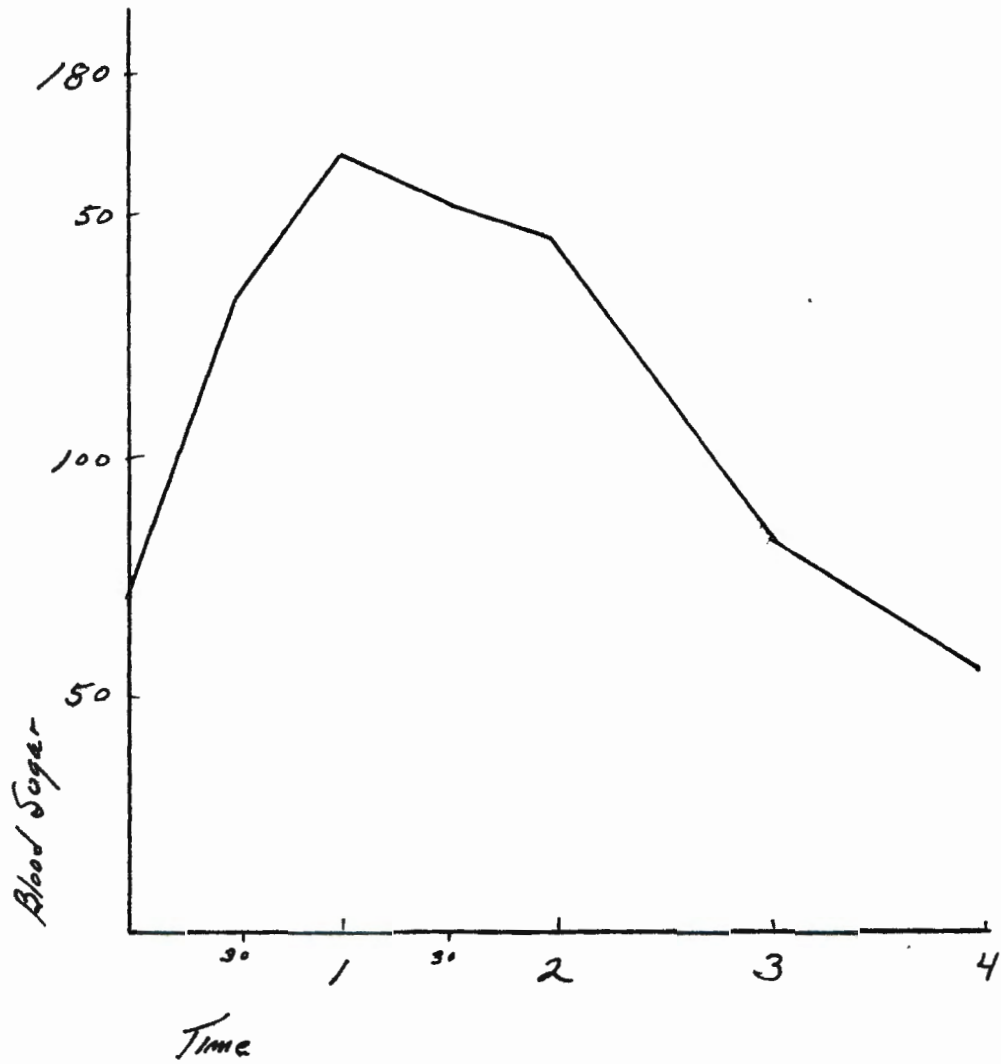
Table 11

switched to substance 60-P. She was examined after 23 days on 60-P when there appeared to be increased deep tendon reflexes. Gait and facial movements were the same as when previously examined. The tremor was quite marked and was present in the legs and lower jaws. The patient was changed to 61-P at 500 mgms twice a day and re-examined 15 days later at which time she appeared to have a more severe tremor.

This patient's tremor seemed to become worse under stress situations and no difference could be detected in the effect of the drugs 60-P and 61-P.

Case 2 This patient is a 71 year old white female who began to have trembling of the hands in 1957, which was aggravated by nervousness. In 1959 the patient was diagnosed as paralysis agitans and treated with Artane and Benadryl. She was examined by myself on December 1, 1960, and found to have reduced facial motility, steppage gait without associated arm movements, and a tremor of the tongue and left arm, and stiffness of the

Case 2



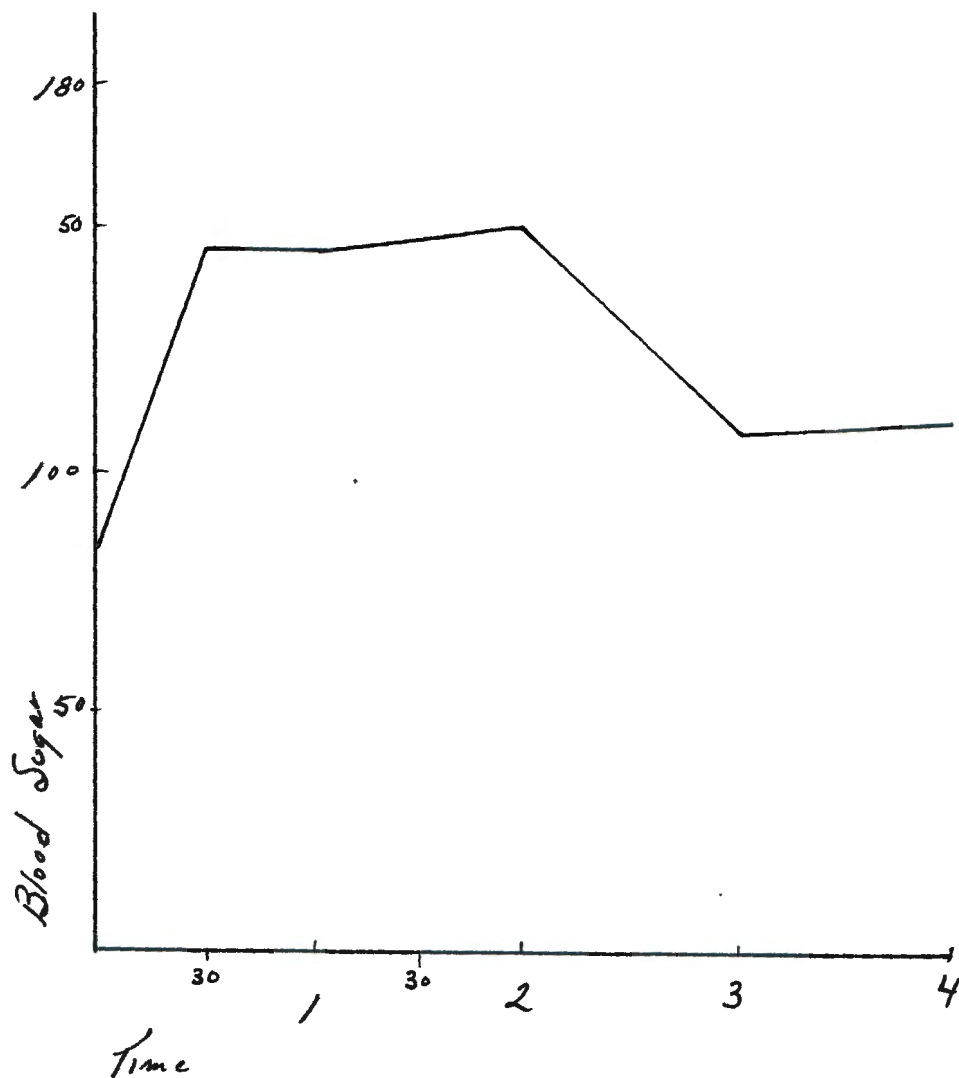
Glucose Tolerance Test

Table 12

low back. The patient was re-examined after 21 days and after this length of time on 500 mgms of 60-P, the tremor had not changed; She thought it was easier to arise from a chair, but no other effect was apparent. The patient was put on 61-P and re-examined in 14 days when the only change noted was a difficulty in arising from a chair. The patient was then started on Artane (2 mgms) and Benadryl (25 mgms) three times a day, and 500 mgms a day of 61-P and re-examined in 7 days. At this time she seemed more forgetful but felt more movable. There was no change in the tremor or rigidity. The patient was changed to 500 mgms a day of 60-P and seen in 14 days when at this time the tremor was confined to the left arm and hand , but she still had trouble arising from a chair. This patient had shown a decrease in tremor with 60-P in combination with Artane and Benadryl.

Case 3 A 66 year old negro female who has had paralysis agitans for 23 years. She has had oculogyric crises since

Case 3

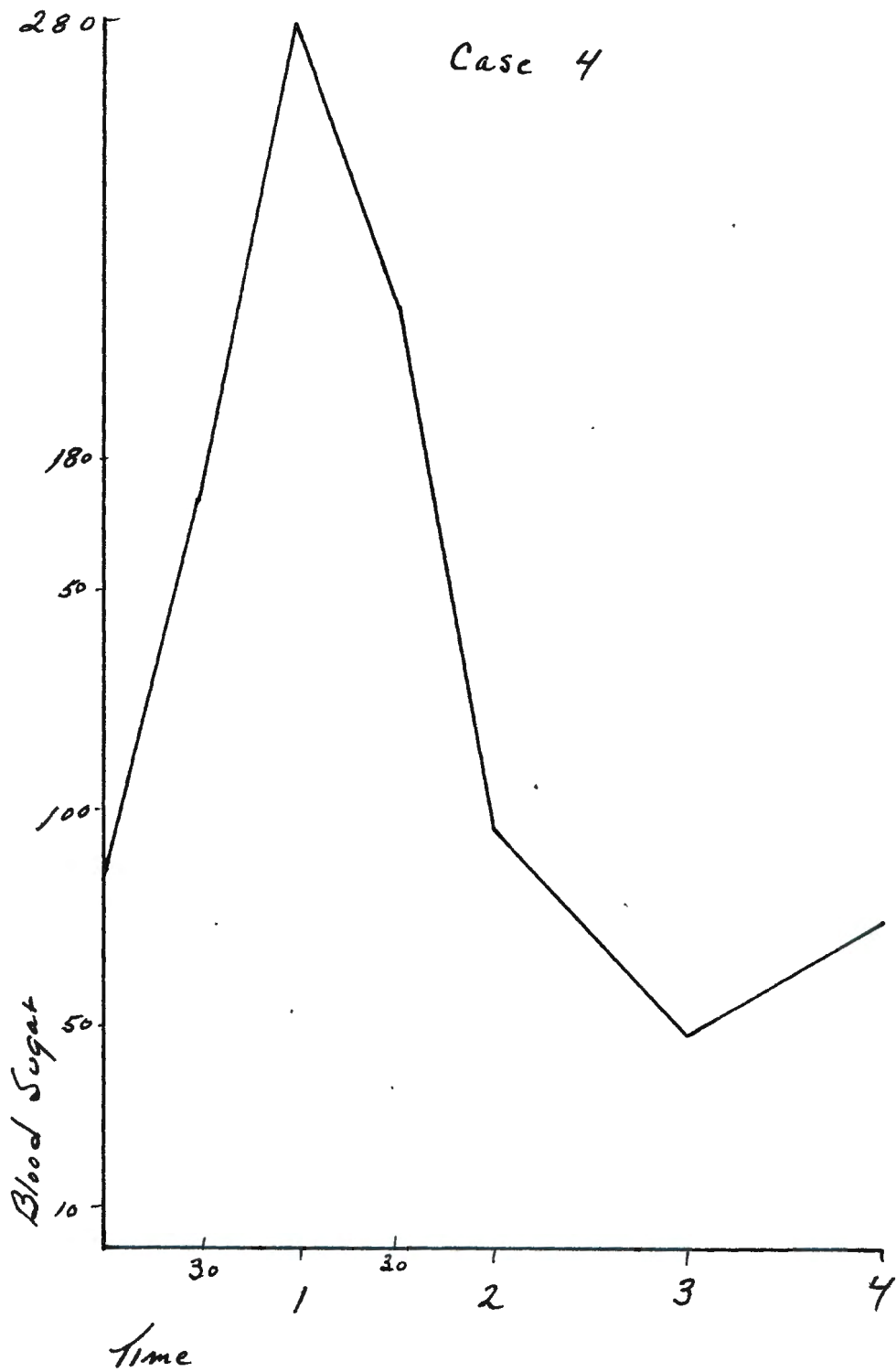


Glucose Tolerance Test

Table 13

1957. She was examined on November 10, 1960, and after an oral glucose tolerance test was told to return, which she did not do. She was on 1 gram of 6l-P for 13 days, 2 mgms of Artane twice a day for 36 days, and 50 mgms of Benadryl twice a day. There was slight improvement of reflexes and tremor over this 49 day interval.

Case 4 A 71 year old white male who has been a house painter since the age of 16 years. He was followed as an out patient at the University of Nebraska Clinics. The patient has a paralysis agitans like tremor for 15 years. When the patient was examined December 8, 1960, he had a tremor at rest in both hands and forearms with reduced strength of the left wrist due to a previous injury, and some cog wheel rigidity of the upper extremities. Position and vibration were reduced in both feet and he had a very fine rapid tremor of the hands that demonstrated itself in his hand writing. The patient was re-examined after 15 days on 6l-P, 1 gram a day, and there was essentially no change from the previous examination.



Glucose Tolerance Test

Table 14

The patient was put on 60-P, 1 gram a day, and in 28 days examination revealed no tremor in the left hand and arm at rest. A fine tremor in the right hand and legs could be palpated. The patient was seen again after 15 days on 60-P, 1 gram a day, and a slight tremor of the left hand was present; cog wheel rigidity was slight.

Case 2 A 51 year old white female who has had paralysis agitans for 26 years. The patient was able to get about until 1955 at which time she had an accident and was confined to a bed. She was followed at the Douglas County Hospital Annex and was first examined on December 21, 1960, and found to have a severe rigidity and plasticity of the extremities and the face which affected the patient's speech. She also had contractures about all major joints. The patient was placed on 1 gram 60-P and re-examined in 15 days at which time no change was noted. The patient was then placed on 2 grams 61-P a day and seen in 13 days with no change noted.

Case 6 A 52 year old white woman who has had paralysis agitans for 35 years, which has been gradually progressive in these years. The patient was followed at the Douglas County Hospital Annex and was examined by me on December 21, 1960 and was found to have rigidity and contractures of the upper extremities. The patient was generally weak with marked atrophy of all muscle groups. She had a tremor at rest of the upper and lower extremities; especially in the lower extremities and becoming more marked with tension. There were contractures about major joints. Position sense was reduced in the lower extremities with some numbness of the fingers of the left hand. The patient's speech was monotone and difficult to understand. Because of the facial rigidity, the patient found it difficult to chew and swallow. She is confined to her bed most of the day. The patient was started on 6l-P, 1 gram a day (table 8) and re-examined in 15 days (table 10) when the tremor was no longer noted, but rigidity was marked

Table 3
Data on Patients with Parkinson's Disease

Case No	Age at Study	Duration	Age of Onset	Type
1	86	17	69	Idiopathic
2	71	4	67	Idiopathic
3	66	23	43	Idiopathic
4	71	15	56	?
5	51	26	25	Post Encephalitic
6	52	35	17	Post Encephalitic

Table 8
Data on Patients with Parkinson's Disease

Case	Date	11	12	12	12	12	12	12	1	1	1	1	1	2	2	
		17	1	8	9	14	23	30	31	14	19	20	21	27	4	11
		60	60	60	60	60	60	60	60	61	61	61	61	61	61	61
1	Orinase	x	-----													
	60-P		x	-----					x	-----						
	61-P								x	-----						
2	60-P				x	-----							x	-----		
	61-P								x	x	-----					
	Artane								x	-----	x	-----	x	-----		
	Benadryl								x	-----	x	-----	x	-----		
3	60-P															
	61-P	x	-----													
	Artane				x	-----			x	-----						
	Benadryl				x	-----			x	-----						
4	60-P							x	-----			x	-----			
	61-P		x	-----											x	-----
5	61-P								xx	-----			xx	-----		
	60-P							x	-----						xx	-----
6	61-P							x	-----						xx	-----
	60-P									xx	-----		xx	-----		

*xx 2 grams

Table 10
Changes in Symptoms of Parkinson's Disease

Case	Drug	D	D	D	G	B	G	D	A	T	O	R	S
1	Orinase	1 Gm	I	21	0	0	0	0	0	0	0	0	0
	60-P	1 Gm	I	23	0	0	0	0	0	0	0	0	0
	61-P	1 Gm	I	14	0	0	0	0	0	0	0	0	0
	60-P	1.5 Gm	I	7	0	0	0	0	0	0	0	0	0
2	60-P	1 Gm	I	21	0	±	0	0	0	-	0	0	0
	61-P	1 Gm	I	14	0	-	0	±	0	0	0	-	0
	Artane	2 mgm tid											
	Benadryl	25 mgm tid		14	0	0	0	0	-	±	0	-	0
	60-P												
3	Artane	2 mgm tid											
	Benadryl	25 mgm tid		7	0	±	0	±	-	-	0	0	0
	61-P												
4	61-P	1 Gm	I	13	0	0	0	0	0	0	0	0	0
	Artane	2 mgm tid							±	±	0	0	0
	Benadryl	50 mgm qid		52	0	0	0	0	±	±	0	0	0
5	61-P	1 Gm	I	15	0	0	0	-	0	0	0	0	0
	60-P	1 Gm	I	28	0	0	0	±	0	0	0	0	0
6	60-P	1 Gm	I	15	0	0	0	-	0	0	0	0	0
	61-P	2 Gm	I	13	0	0	0	0	0	±	±	0	0
	61-P	2 Gm	I	15	0	0	0	0	0	-	-	0	0
6	61-P	1 Gm	I	15	0	0	0	-	-	±	0	0	0
	60-P	2 Gm	I	13	0	0	0	0	0	0	0	0	0
	60-P	2 Gm	I	15	0	0	0	0	0	0	0	0	0

* 0 no change
- degeneration
± improvement

as before. The patient was placed on 2 grams of 60-P a day and re-examined in 13 days. Circum-oral pallor was noted with a slight tremor of the face and hands. No change in rigidity was noted.

Summary

Six patients with multiple sclerosis were given trials on 60-P and 61-P (tolbutamide and a placebo), tolbutamide as shown in (table 2), and diets were altered (table 2). The changes observed were not marked, but there were alterations associated with 60-P and the low carbohydrate diets, and the low carbohydrate-low fat diets. The greatest changes were noted in reflex activity, balance, sensory activity and an uplifting of the mental attitude of these patients.

Six patients with paralysis agitans were given trials on 60-P and 61-P (table 8). Three of the patients had an apparent slight improvement when on 61-P and two patients had slight improvement on Artane and Benadryl. One had

slight improvement on 60-P. All patients on 60-P seemed to have had an improved appetite.

Comment

The significance of this study on the treatment of multiple sclerosis patients with tolbutamide is not clearly understood, but it would seem to suggest that further studies be done under strict control in a hospital. A more accurate control of the patient's diet could be established in a hospital and a varied schedule could be organized in which some patients may use only tolbutamide, while others may have a combination of diet control and tolbutamide. Possibly treatment of the young multiple sclerosis patient over a period of several years would determine a more positive effect. I do feel that this study has enough merit to warrant further searching into the many puzzling aspects of the multiple sclerosis patient.

The significance of this study in paralysis agitans patients would seem to indicate that in dosages up to 2 grams

of 60-P or 61-P there is no clear alteration of tremor or rigidity, but there is an increase in the patient's appetite. It may be that doses of 3 grams of tolbutamide or more may have some effect, but patients on this type of a trial should be hospitalized so that they can be carefully watched for drug toxicity and hypoglycemic reactions.

The drug company that provided the drug and placebo for the double blind study has informed us that 60-P is the placebo, and that 61-P is the tolbutamide. This information would seem to lend support to the observation that these patients were eager for attention and help, and they felt better knowing that something was trying to be done to help them. Response to the placebo was the more marked. It also suggests that the diet portion of the study may be the area that should be explored further.

When giving these patients their medication, I would tell each patient to watch for staggering, dizziness and faintness,

and to take a glass of sugared fruit juice for relief. I
seemed to have more reports of spells with 60-P, rather than
from 61-P, and at the final stages of this study, I felt that
61-P might be the placebo.

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