Summary. Studies on 47 families with 133 children indicate that the major subtypes Rh_1 and Rh_2 are transmitted by means of corresponding allelic genes Rh_1 and Rh_2 which are both dominant over the gene *rh;* and, in addition, that gene Rh_1 is dominant over Rh_2. (A nomenclature for designating the subdivisions of the Rh positive type is proposed).

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The Tocopherol Level in Human Serum During Oral Tocopherol Therapy.*

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In a preceding publication[1] we have described the results of tocopherol studies in human serum by a photoelectric adaptation of the Emmerie and Engel α,α'-bipyridine method.[2] The average tocopherol level for a group of 12 healthy young individuals on an unrestricted diet was 0.96 mg 100 ml of serum. Patients suffering from amyotrophic lateral sclerosis showed slightly lower values within the normal range before tocopherol therapy. The blood level rose after oral administration of the vitamin, but in cases receiving solely intramuscular tocopherol injections a paradoxical drop was noted.

We have now increased the number of cases of amyotrophic lateral sclerosis† and added a group of patients treated orally with tocopherol for myopathies and miscellaneous diseases other than amyotrophic lateral sclerosis.‡ dl-α-Tocopherol acetate in 25 mg tablets was used in all experiments.

The average blood level for 17 untreated cases of amyotrophic lateral sclerosis was 0.67 mg/100 ml and that for 14 miscellaneous myopathies was 0.61 mg/100 ml before treatment. The figures in Tables I and II corroborate the observation that tocopherol ingestion, repeated for several successive days, raises the serum level significantly.

The patients who received treatment are

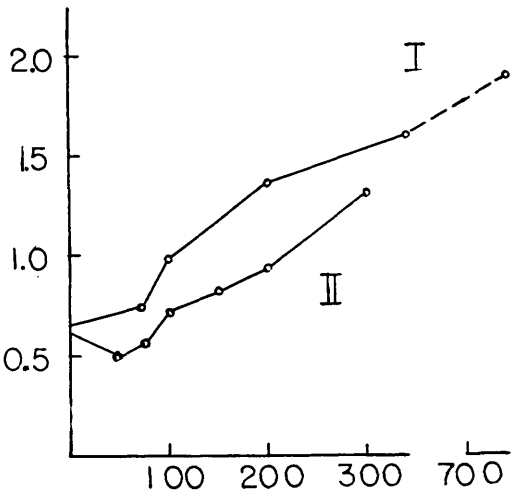

FIG. 1.

Average Serum Tocopherol Level after Administration of Ephynal to Patients with Amyotrophic Lateral Sclerosis (I) and Other Diseases (II).

Ordinates are mg Tocopherol/100 ml serum. Abscissæ are mg Tocopherol administered per day. The points in the graphs represent the average serum tocopherol level for each dosage group. The point given for "0 mg dosage" is the average of all pre-treatment determinations. If the post-treatment level for each dosage group were compared with the pre-treatment level of the corresponding individual group, insignificant changes in the rise of each group would result.

* This work was carried out under grants from the John and Mary Markle Foundation, New York, and the Hoffman La Roche Company, Nutley, New Jersey, who also supplied the Ephynal. We hereby gratefully acknowledge their generous aid.

1 Wechsler, I. S., Gernsheim Mayer, G., and Sobotka, H., PROC. SOC. EXP. BIOL. AND MED., 1941, **47**, 152.

2 Gernsheim Mayer, G., and Sobotka, H., *J. Biol. Chem.*, 1942, **143**, 695.

† A clinical study by I. S. Wechsler, M. R. Sapirstein, and A. Stein of 81 cases, including those studied here, will appear shortly.

‡ We are indebted to the Neurological Service of the Montefiore Hospital for permission to study cases No. 207, 211-213, included in this group.

TABLE I.
Rise in Serum Tocopherol in Amyotrophic Lateral Sclerosis Patients upon Oral Administration.

No.	Sex	Age	Tocopherol content of 100 ml serum: Before treatment mg	After treatment mg	Rise mg	Tocopherol mg per diem	Administered days*	Clinical status
101	M	48	.32	—	—			
102	M	51	.63; .50	—	—			
5	M	47	.69	—	—			
8	M	39	1.15	1.36	0.21	75	1	
103a	M	50	.56	0.20	—0.36	75	8	
104a	F	56†	.40	0.66	0.26	75	4	
			.70	0.74	0.04			
105a	M	42	1.16; .90	0.82	—0.08	100	4	
106a	M	52	.66	0.78	0.12	100	7	
13	M	38	.67	0.90	0.23	100	5	
107	F	37	.74; .80	1.25	0.45	100	4	++
9	F	50	.61	1.20	0.59	100	4	
			.73	0.99	0.27			
106b	M	52	[.78]‡	1.10	0.32	200	9	++
104b	F	56	[.66]‡	1.02	0.36	200	5	
108	F	31	.52; .49	0.90	0.41	200	6	+
105b	M	42	[.82]‡	1.54	0.72	200	6	
109	M	38	.59	1.49	0.90	200	5	+
103b	M	50	[.20]	1.29	1.09	200	6	
110	M	55	.97; .90	2.08	1.18	200	12	
			.66	1.37	0.73			
10	M	43	.55; .53	0.93	0.40	340	8	
6	F	39	.80	2.26	1.46	340	5	++
			.67	1.60	0.94			
11	M	50	.69; .88	[1.70]	[0.82]	[740]	[3]	
				2.00	1.12	740	10	++
2	M	41	—	1.68	—	740	67	++
1	F	48	—	1.71	—	740	23	
7	F	58	—	1.79	—	740	22	
3	M	32	—	2.07	—	740	69	
8	M	39	—	2.14	—	740	28	
			.88	1.90	1.12			
Average of all cases:			0.67	—	—			

The case numbers below 100 correspond to the numbers in Table II of our previous publication.[1]

* Number of days indicates time elapsed from the beginning of administration to the day of determination "after treatment," but treatment was actually often continued beyond that date.

† Diagnosis of No. 104 not definite.

‡ The figures in brackets have been excluded from computations of the total average. In case of duplicate determinations, separated by a few days, the first one has been disregarded in averaging.

\+ = No evidence of progression while under observation.

++ = Temporary improvement or recession of signs and symptoms.

grouped according to the strength of the daily doses. Fig. 1 shows that 75 mg per diem leave the average serum level unaffected. 100 mg a day cause a rise of 0.27 mg in cases of amyotrophic lateral sclerosis, but amounts of 200 mg double the tocopherol titer to

TABLE II.
Serum Tocopherol in Miscellaneous Cases Before and After Tocopherol Administration.

No.	Sex	Age	Diagnosis	Tocopherol content of 100 ml serum: Before treatment mg	After treatment mg	Rise mg	Tocopherol mg per diem	Administered days*
201	F	31	Myopathy	.60; .64	—	—		
202	M	50	Lumbo-sacral radiculitis	.63	—	—		
203	M	42	Lateral sclerosis	.90	—	—		
204	M	55	Lumbo-sacral radiculitis	1.07	—	—		
				.81				
205	M	8	Myopathy	.35; .33	0.50	0.17	50	11
208a	F	32	"	.88	0.69	—0.19	75	4
206a	M	21	Normal	.54	0.59	0.05	75	5
207	M	18	Myopathy	.25	0.42	0.17	75	5
				.56	0.57	0.01		
209a	M	24	"	.80; .51	0.43	—0.08	100	8
210	M	22	"	.46; .79	1.00	0.21	100	5
				.65	0.72	0.07		
211	M	18	"	.52	0.35	—0.17	150	11
206b	M	21	Normal	[.59]‡	0.50	—0.09	150	5
212	F	58	Myopathy	.54	1.60	1.06	150	8
				.53	0.82	0.27		
209b	M	24	"	[.43]‡	0.40	—0.03	200	8
208b	F	32	"	[.69]‡	0.93	0.24	200	4
213	M	33	"	.48	1.49	1.01	200	17
				.48	0.94	0.41		
214	F	47	Diffuse calcinosis	.40; .49	1.32	0.83	300	7
Average of all cases:				.61	- -	—		

values approaching those observed previously[1] with daily doses of 340 mg and 740 mg. The respective increases with 100-300 mg per diem in the miscellaneous group were erratic and their averages distinctly lower than in amyotrophic lateral sclerosis. In 4 individuals (Nos. 103-106) the rise was determined after a first period of 75-100 mg per diem and a second period of 200 mg per diem. The response rose from —0.36 to +1.09, from 0.26 to 0.36, from —0.08 to +0.72 and from +0.12 to +0.32 respectively. Similar experiments on one normal subject (206) and 2 cases with muscular dystrophy (208 and 209) yielded equivocal results.

A comparison of daily dosage and rise in blood level with the temporary improvement, observed during tocopherol administration in amyotrophic lateral sclerosis, shows that such beneficent effects occurred in one of 8 cases receiving 100 mg p.d. or less and in 6 out of 9 cases receiving 200 mg or more. None of 6 cases whose blood level had decreased, or increased by less than 0.40 mg/100 ml serum showed any favorable effect, whereas 7 of 11 cases showed such temporary effects concomitantly with a rise of serum tocopherol by more than 0.40 mg/100 ml. These findings suggest that any further therapeutic trials with oral tocopherol administration in amyotrophic lateral sclerosis should be based on repeated daily dosage of 200 mg or more.

The miscellaneous group is not sufficiently

large to correlate the nature of the response of the blood level with individual disease entities.

We could not detect tocopherol in any of 6 specimens of spinal fluid from amyotrophic lateral sclerosis and other patients.

Summary. In continuation of previous studies, the tocopherol level in the serum of patients with amyotrophic lateral sclerosis and with miscellaneous myopathies was found to average 0.67 and 0.61 mg/100 ml respectively. The response to daily oral administration of 75 to 740 mg tocopherol runs parallel to the dosage and attains levels of more than 2.0 mg/100 ml serum. Temporary favorable effects on the clinical status are only found with doses over 200 mg tocopherol per diem. The spinal fluid does not contain tocopherol.

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Heparin and the Agglutination of Platelets *in Vitro.*

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Heparin inhibits both the coagulation of the blood and the agglutination of platelets. A much higher concentration, however, is required for the latter. Solandt and Best[1] have shown that over 300 mg per kg of body weight must be injected intravenously to prevent the intravascular clumping of platelets. The object of the present study was to determine the minimum amount of heparin that is required for the prevention of platelet agglutination *in vitro.*

Blood was drawn into a dry sterile syringe, and immediately distributed in 1 cc amounts to a series of small test tubes containing 0.1 cc of heparin solution (Roche Organon Liquaemin*) of varying concentrations as recorded in the table. After thorough mixing, the blood was drawn to the 0.5 mark in a red blood cell pipette and the pipette filled with 0.85% sodium chloride solution. The platelet count was made in the usual manner.

A concentration of more than 0.1 mg (or 10 Toronto units) per cc of human blood is required to prevent clumping of platelets. No decrease in the platelet count by heparin as reported by Copley and Robb[2] was observed. Why so much more heparin is required for the prevention of platelet agglutination than for inhibiting coagulation is not clear. Nevertheless, it is well recognized that a definite relationship exists between these two processes. An additional observation in support

TABLE I.
Influence of Heparin on the Platelet Count *in vitro.*

Amt of heparin per cc of blood	Platelet count of human subjects			State of platelets
	I	II	III	
None*	337,000	312,000	278,000	No clumping
0.1 mg	360,000	320,000	286,000	Definite clumping
0.25	372,000	300,000	270,000	No clumping
0.5	320,000	208,000	264,000	" "
1.0	348,000			" "

* 0.1 cc of 3.8% sodium citrate was used.

[1] Solandt, D. Y., and Best, C. H., *Lancet*, 1940, **1**, 1042.

* The Liquaemin was kindly supplied by Edward A. Wickham of Roche Organon, Inc., Nutley, New Jersey.

[2] Copley, A. L., and Robb, T. P., *Am. J. Clin. Path.*, 1942, **12**, 416.