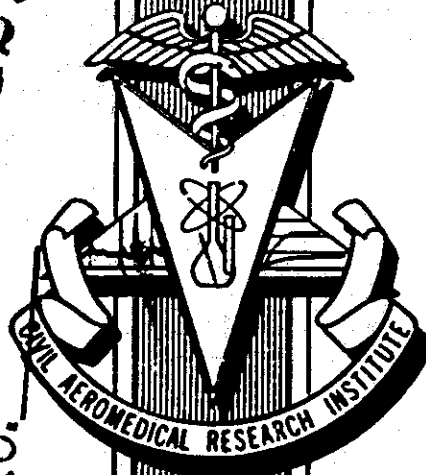


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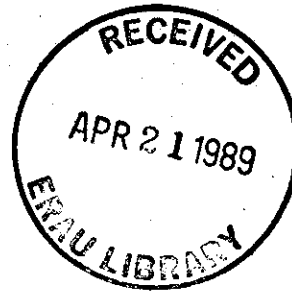
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THE MITIGATION  
OF  
PHYSICAL FATIGUE  
WITH "SPARTASE"



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FEDERAL AVIATION AGENCY  
AVIATION MEDICAL SERVICE  
AEROMEDICAL RESEARCH DIVISION  
CIVIL AEROMEDICAL RESEARCH INSTITUTE  
OKLAHOMA CITY, OKLAHOMA

JULY 1963

<p>Civil Aeronautical Research Institute, Federal Aviation Agency, Oklahoma City, Oklahoma. CARI Report 63-12. THE MITIGATION OF PHYSICAL FATIGUE WITH "SPARTASE" by Francis J. Nagle, Ed.D., Bruno Balke, M.D., Richard V. Ganslen, Ph.D. and Audie W. Davis, Jr., M.D.</p> <p>Pharmacological and clinical observations have indicated that Spartase - the aspartic acid salts of potassium and magnesium - takes part in the intermediary metabolism and moderates physical fatigue. In this study attempts were made to evaluate effects of the drug on work capacity before and after episodes of physically fatiguing exercises. Work capacity was determined by a standardized treadmill test. The test was repeated after the subject had been running cross-country for a period of 60 minutes, and again after another such period of 40 minutes. In this way effects of fatigue upon functional adaptability to stress became apparent. Then, Spartase was taken orally in a prescribed dose for two weeks whereupon the same testing procedure was reapplied. The results indicated that Spartase improved the endurance performance of untrained individuals engaging in extremely fatiguing physical work. It appeared to have no effect on highly trained individuals.</p> <p>1. Stress Physiology 2. Stress Pharmacology 3. Physical Fitness</p>	<p>Civil Aeronautical Research Institute, Federal Aviation Agency, Oklahoma City, Oklahoma. CARI Report 63-12. THE MITIGATION OF PHYSICAL FATIGUE WITH "SPARTASE" by Francis J. Nagle, Ed.D., Bruno Balke, M.D., Richard V. Ganslen, Ph.D. and Audie W. Davis, Jr., M.D.</p> <p>Pharmacological and clinical observations have indicated that Spartase - the aspartic acid salts of potassium and magnesium - takes part in the intermediary metabolism and moderates physical fatigue. In this study attempts were made to evaluate effects of the drug on work capacity before and after episodes of physically fatiguing exercises. Work capacity was determined by a standardized treadmill test. The test was repeated after the subject had been running cross-country for a period of 60 minutes, and again after another such period of 40 minutes. In this way effects of fatigue upon functional adaptability to stress became apparent. Then, Spartase was taken orally in a prescribed dose for two weeks whereupon the same testing procedure was reapplied. The results indicated that Spartase improved the endurance performance of untrained individuals engaging in extremely fatiguing physical work. It appeared to have no effect on highly trained individuals.</p> <p>1. Stress Physiology 2. Stress Pharmacology 3. Physical Fitness</p>
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***Biodynamics Branch***

**63-12**

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## THE MITIGATION OF PHYSICAL FATIGUE WITH "SPARTASE"

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### ABSTRACT

Pharmacological and clinical observations have indicated that Spartase — the aspartic acid salts of potassium and magnesium — takes part in the intermediary metabolism and moderates physical fatigue. In this study attempts were made to evaluate effects of the drug on work capacity before and after episodes of physically fatiguing exercises. Work capacity was determined by a standardized treadmill test. The test was repeated after the subject had been running cross-country for a period of 60 minutes, and again after another such period of 40 minutes. In this way effects of fatigue upon functional adaptability to stress became apparent. Then, Spartase was taken orally in a prescribed dose for two weeks whereupon the same testing procedure was reapplied. The results indicated that Spartase improved the endurance performance of untrained individuals engaging in extremely fatiguing physical work. It appeared to have no effect on highly trained individuals.

Fatigue is a normal consequence of mental and physical work and apparently an essential factor in the establishment of the rhythmic cycle of wakefulness and sleep. It is accompanied by biological properties adverse to good performance capacity. Although these properties are reversible under conditions of adequate rest, man has long sought for physical or chemical means to prevent or moderate fatigue induced disturbances in the organism, thus extending periods of work at peak efficiency.

One of the drugs reputed to moderate physical fatigue is Spartase\* — the trade name for the potassium and magnesium salts of aspartic acid. Aspartic acid is a non-essential glyco-genic amino acid, playing some role in protein metabolism where urea is the end product. It is, according to Ratner," the specific nitrogen donor in the conversion of citrulline to arginine which occurs anaerobically in the presence of magnesium ions and adenosine triphosphate in the ornithine cycle. Of possible significance

is the fact that the ornithine cycle is related to the energy producing Krebs cycle as schematically shown in Figure 1.

Clinical and laboratory investigations have indicated that potassium and magnesium aspartates can moderate physical fatigue. Kruse" and Vial" have reported reductions in the subjective symptoms of fatigue, the former treating patients with Spartase, the latter administering it to trained athletes.

Extensive work has been reported in which the electronic rheotome was used as a tool for performance evaluation. The rheotome permits muscle excitation by electric stimulation of the proper motor nerves in designated cutaneous areas, or by stimulation of underlying muscles directly. The relationship of intensity-duration curves for nerve and muscle, which, according to the investigators is characteristic of the fatigue state, has been shown to revert back to normal following treatment with Spartase.<sup>1,2,3,4</sup>

The purpose of this investigation was to study objectively the effect of the drug on work capacity by measuring the physiological

\*Potassium and magnesium aspartates used in this study were provided by Wyeth Laboratories as Spartase.

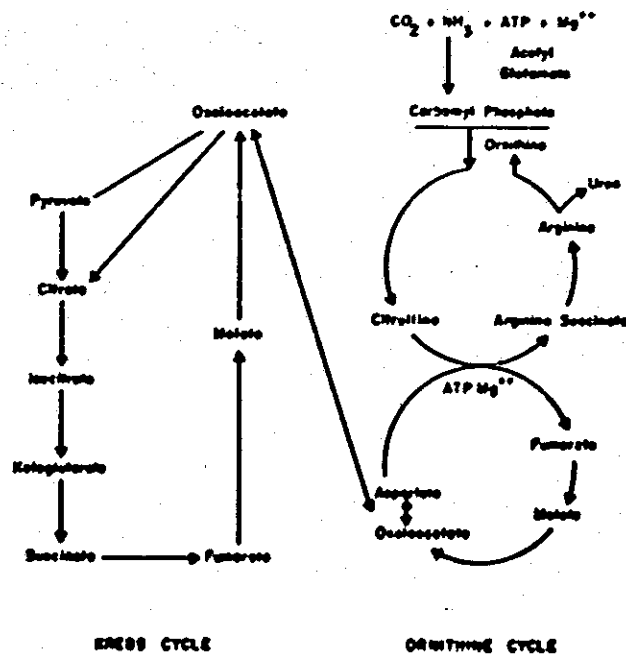


Figure 1. - This schematic illustrates the involvement of Aspartate in the Ornithine Cycle and the linking of the Ornithine Cycle with the Krebs Cycle.

adjustments to increasingly demanding physical work under normal conditions and in various states of fatigue.

### PROCEDURE

The experimental plan called for the evaluation of work capacity under normal conditions and at two different stages of induced physical fatigue. This was accomplished by determining the biodynamic potential of four subjects on a treadmill by means of a Work Capacity Test (WCT) described elsewhere.<sup>10</sup> The subjects were thoroughly rested and in a post-absorptive state.

Immediately following the first test (WCT I) the subjects ran for 60-minutes on a country road, attempting to cover the greatest possible distance during that time period. This activity caused a certain amount of physical fatigue which was made evident in WCT II administered immediately after returning from the 60-minute run. After another best-effort run of 40 minutes duration the fatiguing consequences

of the overall effort were evaluated in a final WCT III.

Four normal subjects of 21, 32, 38 and 55 years of age participated in the study. Subject A (21) was a college student trained for competitive cross-country running. Subject B (38) followed a regular training regimen, running from one to four miles three times each week. Subject C (32) played occasional tennis but had not participated in physical exercises of any significance for four weeks prior to the experiments. Subject D (55), out of regular training for several months, ran distances of 2-3 miles once or twice a week.

For Subject C the two periods of road-running were replaced by equivalent but more readily controllable work-outs on the treadmill. During the treadmill tests pulse rate, blood pressure and pulmonary ventilation were measured at regular intervals and the oxygen intake and carbon dioxide output were determined at the crest level. The total energy expenditures during the running periods were estimated from the oxygen requirements for given running

velocities.<sup>66</sup> In the treadmill experiments, the speed and slope of the belt served as factors for the estimation of oxygen intake and total energy out-put.<sup>67</sup>

Considering the possibility of changes in orthostatic tolerance due to physical fatigue, tilt table tests were carried out on each subject before the first and following the last WCT of each experimental series. During 5 minutes in the supine position, for 7 minutes tilted footward to 60 degrees and for 3 minutes following the return to the horizontal, pulse rate and blood pressure were measured in half-minute intervals. In addition, one-lead ECG tracings from chest electrodes were obtained during the tilt and exercise experiments.

After the "control" responses to this complete test procedure had been established, the Spartase regimen was begun. Four tablets of 250 mg potassium aspartate and 250 mg magnesium aspartate each were taken daily for a period of one week by Subject D and for two weeks by the other three subjects. Then, the entire testing procedure was repeated in a second series, under external environmental conditions nearly identical to those of the first series as shown in Table I.

## RESULTS

The course of the entire exercise procedure and the functional adjustments observed during its various phases are shown by the data of Subject B in Figure 2. The subject's cardio-respiratory responses to the gradually increasing energy demands, the latter expressed in amounts of oxygen required per unit of body weight, provide a proper accounting of his functional reserves and limitations during each of the Work Capacity Tests. In this particular case, the subject attained a maximum oxygen intake of 44.2 ml/kg/min in the first "control" test and then worked at an estimated 88 per cent of this potential capacity during the 60-minute run. The physical fatigue resulting from this effort caused a considerable reduction of work capacity in WCT II. Accordingly, the average performance during the second steady state period of work, running 40 minutes, was lower than during the first period. The maximum oxygen intake at the end of the third WCT was only 72 per cent of that attained in WCT I. Although, for any given workload, the pulmonary ventilation increased with accumulating fatigue, the peak volume at the end

TABLE I

AIR TEMPERATURE AND RELATIVE HUMIDITY DURING THE OUT-DOOR RUNS:

SUBJECT	CONTROL EXPERIMENTS		SPARTASE EXPERIMENTS	
	TEMP. °C	HUMIDITY %	TEMP. °C	HUMIDITY %
A	30	88	32	49
B	32	44	31	81
D	32	80	31	47

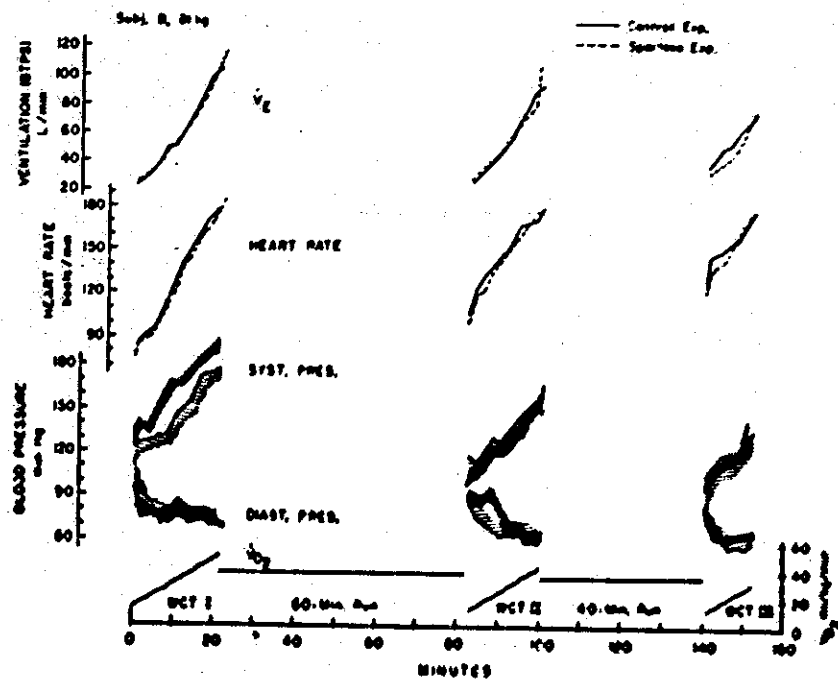


Figure 2. - Physiological data recorded during work capacity tests in Control and Spartase series of experiments on well trained subject.

of each successive test was lower than in the previous test. For this experimental subject the values were 104, 94, and 78 l/min (BTPS) for WCT I, II and III, respectively.

Figure 2 also shows the test results after the administration of Spartase. The subject's functional response pattern as well as the performance capacity in all three tests were nearly identical. However, in case of Subject D (Figure 3) Spartase appeared to have altered the pattern of cardiorespiratory adjustments in response to the same energy demands. Hemodynamic conditions were apparently more economical (lower pulse rate and pulse pressure) and the ventilatory efficiency was certainly improved in WCT II and III (less volume of air moved at same oxygen requirement). The subject was not only able to perform more work during the 40-minute run, but also demonstrated a considerable improvement of work capacity in the last test.

The essential performance data of all four subjects are shown in Table 2. Because body weights changed considerably during the experimental procedure, the minute values for

maximum oxygen intake (in the work capacity tests) and for the average oxygen requirements during the running periods were presented in milliliters per kilogram of body weight. Since maximum oxygen intake served as the main performance criterion, the various work levels attained were expressed in per cent of the oxygen intake achieved in the first "control" test.

Considering the decline of performance from WCT I to WCT III as most significant for the assessment of "physical fatigue," the results obtained in the "control" tests revealed for all four subjects, a decrease to 64-72 per cent of the original work capacity as a consequence of the preceding physical efforts. In the Spartase experiments the two well-trained individuals experienced essentially the same performance deterioration as in the "control" experiments. The two physically less active subjects, however, demonstrated an increase of functional and metabolic reserves in the final test, their maximum oxygen intake being 33.3 for Subject C and 36.5 ml/kg for Subject D compared to 28.8 and 27.9 ml/kg, respectively, in "control"

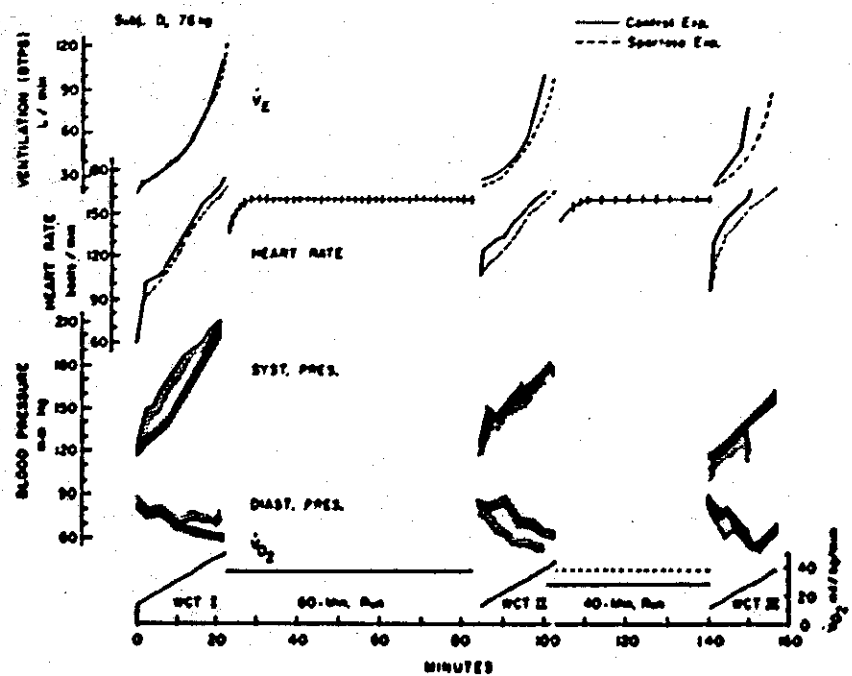


Figure 3. - Physiological data secured during work capacity tests in Control and Spartase series of experiments on untrained subject.

TABLE 2

	Weight		VO <sub>2</sub>		Performance		Weight		VO <sub>2</sub>		Performance	
	kg		ml/kg/min		%		kg		ml/kg/min		%	
	pre	post	pre	post	pre	post	pre	post	pre	post	pre	post
SUBJECT 2 <sup>a</sup>						SUBJECT 3 <sup>a</sup>						
WCT I	64.6	64.3	37.8	36.2	100	98	61.7	60.3	44.2	46.1	100	100
60-min. run	--	--	19.8	18.5	88	84	--	--	37.9	38.8	88	87
WCT II	62.8	62.4	49.6	46.2	98	88	78.8	78.0	40.9	38.8	98	98
40-min. run	--	--	38.8	36.7	87	82	--	--	38.4	38.4	88	88
WCT III	61.2	60.6	37.8	36.4	88	87	77.8	78.8	34.7	38.8	72	88
SUBJECT 2 <sup>b</sup>						SUBJECT 3 <sup>b</sup>						
WCT I	71.7	71.3	40.0	44.7	100	111	78.2	77.1	43.8	44.8	100	100
60-min. run	--	--	30.8	30.8	78	78	--	--	38.8	38.8	84	84
WCT II	70.8	70.8	33.8	34.7	88	88	73.8	73.8	37.2	38.8	88	88
40-min. run	--	--	24.8	24.8	81	81	--	--	27.3	38.8	83	88
WCT III	68.8	68.7	26.8	33.3	88	81	72.8	73.4	27.8	34.8	84	84

Individual values for body weight, oxygen intake (mean VO<sub>2</sub> in the Work Capacity Test and average VO<sub>2</sub> during running) and performance relative to the work capacity established in WCT I of the experimental control series (pre and post Spartase).



WCT III. The improved work capacities of Subjects C and D were also expressed in greater total energy expenditures (See Table 3). Thus, while the untrained subjects undoubtedly benefited from the drug, the application of Spartase in the two subjects who were trained for peak performance in running appeared to upset slightly the adequate adjustments for severe physical efforts. These differences in

response were certainly not the result of training or motivating factors nor, apparently, the result of climatological factors (See Table 1). In the case of Subject C, all experimental work was done in the laboratory under controlled environmental conditions, and in the other experiments temperature, humidity and solar radiation were nearly the same.

TABLE 3

SUBJECT	ESTIMATED TOTAL ENERGY EXPENDITURE			
	CONTROL EXPERIMENTS		SPARTASE EXPERIMENTS	
	Energy Exp. kcal.	Duration Min.	Energy Exp. kcal.	Duration Min.
A) WELL	2001	170	1979	168
B) TRAINED	1963	161	1947	150
AVERAGE :	2032	160.5	1963	159
C) LESS -	1208	139	1304	147
D) TRAINED	1629	147	1915	166
AVERAGE :	1410	143	1605	161.5

### TILT TABLE TEST

The orthostatic tolerance tests revealed similar reaction patterns in all four subjects. The group averages of blood pressure and pulse rate, presented in Figure 4, show that, in the "control" experiments, the pre-exercise tilting from the supine position to a 60-degree incline caused a slight fall of blood pressure from an average of 124/82 to 120/83 mm Hg accompanied by a rise in pulse rate from 59 to 67 beats per minute. After the fatiguing exercise, during a period of recovery, the changes were more impressive, the blood pressure declining from 118/83 to 93/76 mm Hg while the pulse rate increased from 103 beats per minute to 126 as an average for the 7-minute period of tilt.

Thus, orthostatic tolerance appeared definitely affected by physical fatigue. In the "Spartase" experiments the peripheral neuro-

circulatory responses to the postural changes were nearly identical. This might indicate that in both experimental situations physical fatigue had developed to an identical extent, or that the tilt table tests were not specific enough for detecting more subtle differences in accumulated fatigue.

### ECC

Figure 5 shows a representative recording of the ECG taken at rest and during exercise before and after Spartase. There was no indication of changes in the ECG that might be attributable to Spartase.

The fatigue effect occurring with work in each series of tests is apparent in comparing the 10th minute tracings for WCT I and III. The WCT III tracing made at a metabolic rate of 8 times the resting level closely resembles the peak minute tracings of WCT I made at 12 times the resting metabolic level.

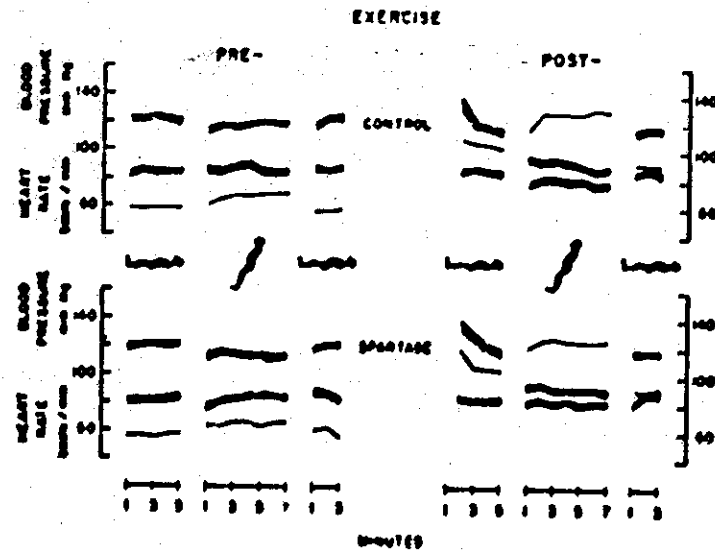


Figure 4. - Average systolic and diastolic blood pressure and pulse rates of 4 subjects during the orthostatic tolerance tests, before and after exercise, in the Control and Spartan series of experiments.

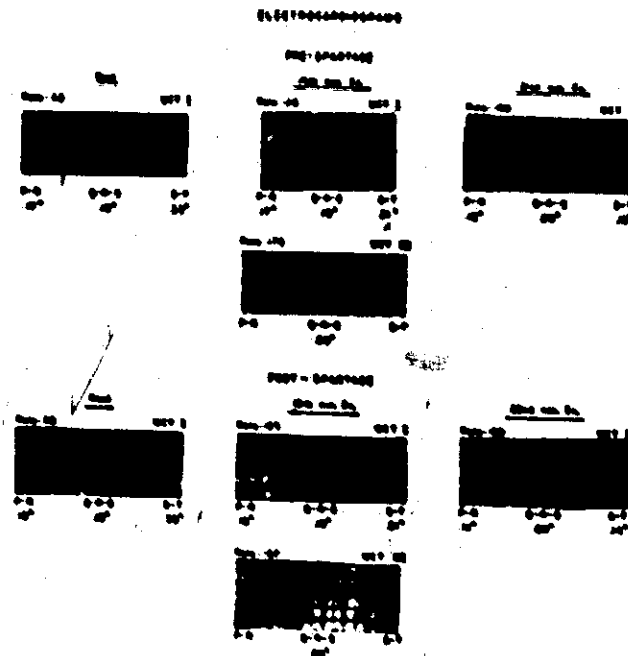


Figure 5. - ECG tracings obtained during work capacity tests in Control and Spartan series of experiments.

## DISCUSSIONS

Improved swimming performances of rats treated with Spartase were reported by Laborit, et al.<sup>10</sup> and Rosen et al.<sup>11</sup> The latter group of investigators made the following observations: The performances observed in 36 control rats appeared to divide them into two major groups, one of lower and one of higher survival capability in endurance swimming. In another experimental series with 36 rats treated with Spartase, this differentiation did not occur and the mean swimming time of this group exceeded that of the control rats. The investigators concluded that the animals of initially low performance capacity were favorably affected by this drug.

A similar response pattern seems apparent in this study with humans. A fatigue mitigating effect of Spartase was observed in the two untrained subjects when their cardiorespiratory and metabolic functions were severely taxed in extended physical efforts. After the administration of Spartase, Subjects C and D expended 100 to 300 kilocalories of additional energy under conditions of near-exhaustion and still scored considerably better in the final performance tests. The two-trained subjects,

on the other hand, showed only slight quantitative changes in performance and no qualitative changes in the fatigue pattern of function response to the test work. Whatever role Spartase may play in intermediary metabolism it contributes nothing to the metabolic capability of the trained individual. Evidently, the trained organism has attained a point of optimum coordination of functional and metabolic adjustments that cannot advantageously be affected by this drug.

We can only speculate on the mechanism involved in mitigating the fatigue of the untrained individuals. A more economical respiratory action is a possibility suggested by the work of Laborit and others.<sup>10</sup> They found reduction of CO<sub>2</sub> in plasma and expired air of hypercapnic dogs treated with magnesium and potassium aspartates. This reduction supposedly occurred as CO<sub>2</sub> and NH<sub>3</sub> were utilized in the ornithine cycle. In the case of Subject C on whom periodic measurements of CO<sub>2</sub> in expired air were made, there was an indication of reduced CO<sub>2</sub> production after the administration of Spartase. This is shown in the data of Table 4. While these data are not conclusive, they are in the direction expected from

TABLE 4

### EXPIRED VOLUME OF CARBON DIOXIDE ml/kg/min — Subject C

Min.	WCT I		WCT II		WCT III	
	Pre-Sp.	Post-Sp.	Pre-Sp.	Post-Sp.	Pre-Sp.	Post-Sp.
2	9.5	11.1	13.4	13.4	12.0	10.6
6	18.5	18.4	17.6	17.1	17.2	16.4
10	24.2	24.0	26.0	23.5		
14	31.2	29.9				
18	42.6	40.1				

Laborit's work. Respiratory center activity during work might have been diminished because of lower blood CO<sub>2</sub> content. Greater economy in the respiratory effort did occur in the cases of Subjects C and D, following Spartase. Both subjects showed sizeable reductions in ventilation at identical workloads, indicating greater ventilatory efficiency since the oxygen requirements remained the same.

The limitations of this study preclude any generalizations about the anti-fatigue effects of Spartase. However, the results, showing a fatigue mitigating effect in some individuals, are of sufficient interest to justify a more detailed study of its role in affecting respiratory gas exchange and intermediary metabolism during prolonged severe stress.

The authors gratefully acknowledge the technical assistance of Wilbur L. Smith and Kamal Shanbour.

#### SUMMARY

Some experimental and clinical investigations have shown that Spartase — the potassium and magnesium salts of aspartic acid — has a mitigating effect on physical fatigue.

It was the purpose of this study to evaluate the effects of the drug on the work capacity of four men before and after episodes of physically fatiguing exercises. Work capacity was determined on the treadmill using the standardized procedure of gradual minute-by-minute increases of slope at constant walking speed. The test was repeated after the subject had been running cross-country for a period of 60 minutes, and again after another such period of 40 minutes. In this way effects of fatigue upon functional adaptability to stress became apparent. After control data had been established, Spartase was taken orally in recommended dosages for two weeks, whereupon the same complex testing procedure was repeated.

The performances of two well-trained individuals appeared to be unaffected by the drug. Two other individuals, who did not train regularly appeared to benefit from the Spartase medication. After Spartase these subjects expended 100-300 kilocalories of additional energy under conditions of near-exhaustion, and still scored considerably better on the crucial

last performance tests.

The results indicated that Spartase was effective in mitigating physical fatigue in untrained individuals engaging in strenuous work. It appeared to have no effect on trained individuals.

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