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Acceleration Protection by Means of Stimulation of the Reticulo-Endothelial System

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SUMMARY

1. Protection of an animal against acceleration stress is usually accomplished by means of environmental alterations. However, under identical environmental conditions there are important intrinsic factors that enable some subjects to withstand acceleration to a much better degree than others. In the past, it has been possible to increase the resistance of the rat to 20 positive G acceleration by means of conditioning or hypophysectomy. Another method, increasing an animal's natural resistance to stress by means of stimulation of the reticulo-endothelial system, is presented here.

2. Reticulo-endothelial stimulation, by means of 10 daily consecutive intraperitoneal injections of bacterial endotoxin in doses of 100 to 1200 μgms, increased the median survival time of 122 rats undergoing 20 positive G acceleration from a control level of 9.7 min to 14.2 min, an increase of 47%. One group of 48 rats after such a regime had a median survival of 23.6 min compared to a control value of 11.3 min, a 112% increase.

3. The increase in acceleration tolerance by endotoxin injection is dose dependent since five injections of endotoxin of lower doses (up to 700 μgms) was not consistently effective. The type of endotoxin utilized as the stimulating substance did not alter the experimental results. Zymosan, a yeast polysaccharide administered intravenously, an alternative method to stimulate the RES, also was effective in increasing resistance to acceleration.

4. In certain groups of animals RES stimulation was ineffective, regardless of endotoxin dosage. It was noted that these groups originally had a significantly decreased resistance to acceleration. It was concluded that RES stimulation is effective only in prolonging survival in those animals with a normal or increased resistance to acceleration before stimulation.

5. Blockade of the RES decreases the percent of animals in a population with prolonged survival but does not greatly effect the median survival, suggesting that blockade also effects only those animals with normal or increased resistance. It is suggested that rats with diminished resistance have a non-reversible RES blockade.

6. Conditioning, hypophysectomy and RES stimulation all may increase resistance to acceleration by similar mechanisms since all are concerned with steroid metabolism and its regulation of cellular metabolism.

7. When more potent, less toxic stimulating substances are available, RES stimulation may prove valuable in aerospace ventures since it is not only effective in increasing resistance to acceleration stress, but it would be expected to be effective in tolerating other stresses which may be encountered, such as vibration and X-irradiation.

TABLE OF CONTENTS

	Page
SUMMARY	ii
INTRODUCTION	1
RETICULO-ENDOTHELIAL SYSTEM	1
METHODS	3
RESULTS	6
DISCUSSION	13
REFERENCES	17

LIST OF TABLES

Table	Title	Page
I	Anatomy of the reticulo-endothelial system	2
II	Methods to alter the function of the reticulo-endothelial system	4
III	Results of all experiments of rats with reticulo-endothelial system stimulation undergoing 20 positive G acceleration	7
IV	Summary and evaluation of different factors in the experiments of rats with reticulo-endothelial system stimulation undergoing 20 positive G acceleration	8

LIST OF FIGURES

Figure	Title	Page
1	The effect of RES stimulation on survival to 20 positive G acceleration of all rats given 10 injections of endotoxin	10

LIST OF FIGURES

Figure	Title	Page
2	The effect of RES stimulation on survival to the 20 positive G acceleration of rats with some resistance to acceleration before stimulation (Expt. 6)	12
3	The effect of RES blockade on survival to 20 positive G acceleration	14

INTRODUCTION

Many methods have been studied to improve an animal's resistance to withstand acceleration stress. Most of these consist of alteration in the subject's environment. Examples would be G suits, contour couches, and underwater tanks, all of which are designed to maintain the body's position or venous return while undergoing the acceleration. Since further progress along these lines well may be approaching a point of diminishing returns, it is necessary to look for new methods of acceleration protection.

There are important "host" factors operating in resistance to acceleration, as is demonstrated by the wide range of acceleration tolerance among identical subjects under identical conditions. The factors responsible for these differences are for the most part unstudied and undefined.

Early attempts to increase an animal's resistance to acceleration utilized various drugs (1, 2) embracing the entire pharmacopeia. None has met with much success to date, although Polis (3) has some encouraging results with Lucidril. Another method is that of conditioning — exposing the animal to repeated increments of the stress until it builds up tolerance. This has proved successful (4) under certain conditions but has been tedious and resulted in a high percent of deaths during the conditioning. The mechanism of action in conditioning remains obscure.

A third method, hypophysectomy (5), has been very successful in increasing the acceleration tolerance of these animals. This effect is negated by simultaneous adrenalectomy. This radical departure from the physiological state has enabled rats to withstand acceleration up to three times longer than control animals. Although this approach offered no practical solution, it yielded considerable information into the biochemical factors operating in acceleration protection.

Additional information was sought which could possibly lead to procedures for developing enhanced tolerance to acceleration stress. By increasing an animal's resistance to acceleration by stimulation of the reticulo-endothelial system, another physiological component concerned in acceleration tolerance was revealed.

RETICULO-ENDOTHELIAL SYSTEM

The reticulo-endothelial system (RES) is a group of widely scattered cells within the capillaries and tissue spaces, including (Table I) hepatic Kupffer cells, lymphoid elements of marrow, spleen and lymph nodes, sinusoidal endothelial cells, and circulating lymphocytes and

TABLE I

ANATOMY OF THE RETICULO-ENDOTHELIAL SYSTEM *

Fixed Cells	Free Cells
1. Hepatic Kupffer Cells	1. Blood Lymphocytes
2. Sinusoidal Endothelial Cells	2. Blood Monocytes
3. Bone Marrow	3. Tissue Lymphocytes
4. Lymph Nodes	4. Tissue Histiocytes
5. Spleen	5. Pulmonary Septal Cells
6. Thymus, Adrenal, Ovary	

FUNCTIONS OF THE RETICULO-ENDOTHELIAL SYSTEM

1. Phagocytosis
2. Antibody Formation
3. Detoxification
4. Steroid Metabolism
5. Lipid Clearance
6. "Non-Specific" or "Natural" Resistance

* After Bailliff (6)

monocytes (6). These cells function to protect the body from noxious elements, both endogenous and exogenous, through such functions as phagocytosis, antibody formation, detoxification, steroid metabolism, lipid clearance, and "natural resistance" (7).

Upon entry of a foreign substance such as bacterial endotoxin, these cells enlarge and multiply, protecting the body and enabling it to withstand better a second invasion (8). By gradually increasing the amount of the challenging agent in successive injections, one can cause the body to develop tolerance to a fatal dose of the agent.

During this state of heightened resistance, the animal, in addition to being able to survive a fatal dose of endotoxin, has an increased resistance to many types of stresses, including drum trauma (9), hemorrhagic shock (9), X-irradiation (10), and tumor invasion (11). This resistant state can be brought about by use of endotoxin, intravenous particulate matter, or zymosan and can be prevented or abolished by overloading the system with any of these agents, by administration of steroids or by overwhelming infection (Table II). Because of the non-specificity of the inducing agent and the wide spectrum of stresses which can be protected against, this type of resistance is labelled "natural resistance". This heightened natural resistance following RES stimulation has been utilized to increase the rat's ability to withstand acceleration.

METHODS

Male Sprague Dawley Rats weighing 150 grams were obtained from Hormonal Assay Laboratories, Chicago, Illinois, and were allowed to acclimatize in the animal colony for 1 to 3 weeks before use by which time they weighed 250 to 325 grams. The rats were fed Purina rat chow and water ad libitum.

Tolerance to acceleration was measured on the 8-foot radius animal centrifuge by a method developed at the Aviation Medical Acceleration Laboratory (5,12). This consists of centrifuging rats at 20 positive G (acceleration directed from head to foot) and recording the ECG of the rats by means of two wires attached to the animal's back and chest. The cardiac potential is amplified 3000 times by means of a transistor amplifier mounted on the centrifuge. The amplified signal is then brought through slip rings to an amplifier-recorder and a continuous tracing of the rat ECG is obtained.

TABLE II

METHODS TO ALTER THE FUNCTION OF THE

RETICULO-ENDOTHELIAL SYSTEM

Stimulation	Inhibition
1. Endotoxin Injection	1. Intravenous Particulate Matter - Large Doses
2. Intravenous Particulate Matter - Small Doses	2. Steroid Hormones
3. Zymosan	3. Overwhelming Infection
4. Restim	
5. Stress Conditioning (?)	

PARAMETERS OF STRESS WHICH MAY BE MODIFIED BY

RETICULO-ENDOTHELIAL STIMULATION

1. Endotoxin Injection	5. Hemorrhage Shock
2. Bacterial Invasion	6. Tumor Invasion
3. X-Irradiation	7. Acceleration Stress
4. Drum Trauma	

Upon onset of acceleration, there is a period of irregular electrical activity resembling fibrillation. After 50 to 100 seconds, the rat recovers a normal regular heart rate of 8 to 12 beats/sec and maintains this until "fibrillation" recurs. This fibrillation usually terminates after 30 to 60 seconds followed by marked slowing of the heart rate. The end point of survival is considered to be that time when the heart slows to 2 to 3 beats/sec for 5 sec. If the centrifuge is stopped at this point, about one half the rats survive so this is considered to be a valid physiological end point (12). A small percentage of animals (3 to 5%) never recover from the initial fibrillation and die within 180 seconds. Since these animals usually demonstrate pre-existing pathology such as pneumonia and since they are equally divided among controls and test groups, they were discarded from consideration.

Reticulo-endothelial stimulation was accomplished, in most of the experiments, by injection of bacterial endotoxin (13). These endotoxins, made by the procedure of Landy, et al (14) by the Difco Co., Detroit 1, Michigan, were dissolved in sterile 0.15 M. NaCl and injected intraperitoneally into the rats. Three types of endotoxins, Salmonella Typhosa, Escherichia Coli and Staphylococcus Aureus were utilized in different injection schedules, ranging from 5 to 10 consecutive days in doses of 50 to 100 μgms initially, increasing up to final doses of 350 to 1200 μgms. The most effective, and thus the final schedule was 10 consecutive injections of 100, 200, 300, 400, 500, 600, 700, 800, 1000, 1200 μgms.

The animals were centrifuged 48 to 72 hours after the final injection. This choice was made after preliminary experiments and from the work of others (9). The protection resulting from RES stimulation by endotoxin has an onset at 24 hours, reaches maximum at 48 to 72 hours and has disappeared by 120 hours.

The RES of the nine animals was stimulated by the yeast polysaccharide zymosan (Standard Brands, Inc., New York City) (15). One injection of zymosan dissolved in sterile 0.15 M.NaCl was given intravenously via a tail vein daily for two days at a dose level of 1 mgm/100.gms of body weight. These animals were centrifuged 24 hours after the final injection, since the onset of action is more rapid than that of endotoxin.

RES blockade, a state of impaired function of the system, can be induced by overloading the cells with particulate matter; this was achieved by intravenous injection of saccharated iron oxide (Proferrin, Sharpe and Dohme, Inc., Philadelphia) 8 mgm/100 gm of body weight. Such treatment has been shown to markedly decrease phagocytic activity (9), and presumably other RES functions.

No animals died as a result of any type of injection, either for stimulation or blockade, in the dosages employed. However, the endotoxins were uniformally fatal if given in large doses (4 mgm). An occasional diarrhea and some retardation of growth was found in the endotoxin-injected animals. This was especially notable in those animals given 10 injections of endotoxin. However, there was no correlation between weight and survival per se. No other toxic effects were noted.

The statistical method used to evaluate the validity of the data was the Time-Percent Effect Graphical Technique of Lichtfield (16). The data were plotted as percent survival-versus time on probit-log paper and after determination of the slope, nomographs were utilized to determine whether or not the compared groups of rats were significantly different at the 5% level of confidence.

RESULTS

Eight experiments were done over a period of 10 months, utilizing different doses, injection schedules, and various RES stimulating substances. These experiments are summarized in Table III which presents the survival times when 75, 50 and 25 percent of the animals are alive. The 50% survival is the median survival time and represents the most convenient appraisal of the performance of a group as a whole. The last column gives a semi-quantitative estimate of the results of each experiment, all experiments rated +, ++, +++, being significant at the 5% level, with prolongation of median survival of 1.5 to 3.0 min, 3.0 to 5.0 min, and over 5 min for the +, ++, +++ symbols.

One notes that RES stimulation was accomplished in most of the animals by intraperitoneal injection of endotoxin. As seen in Experiment 5 of Table II, intravenous zymosan is at least as effective as endotoxin, but because of the inconvenience of intravenous injections, further work was not done. This does show that this type of response is not confined to endotoxin.

The results of individual experiments range from no increase of survival over control levels (Experiment 3) to a marked increase of the median survival time (Experiment 6) of over 100%. A summary of all the rats undergoing RES stimulation compared to all the controls is given in Group I of Table IV. The median survival time of 280 RES stimulated rats is 11.5 min compared to a median survival time of 9.9 min for 148 control rats, an increase of 16%, a slight but significant increase.

TABLE III

RESULTS OF ALL EXPERIMENTS OF RATS WITH RETICULO-ENDOTHELIAL SYSTEM STIMULATION UNDERGOING 20 POSITIVE G ACCELERATION

Expt. No.	Date	Stimulating substance	Hours to centrifugation after last injection	No. of injections	No. of animals in group	Avg. weight (gms.)	Range of doses (μ gms)	Survival times (min) at % alive			Evaluation of Results
								$ST_{75\%}$	$ST_{50\%}$	$ST_{25\%}$	
1	2/15/60	Control	--	-	24	---	---	7.9	10.5	12.9	
		E. Coli	72	5	23		50 → 350	9.7	12.4	16.8	+
2	3/1/60	Control	--	-	24	---	---	7.9	10.5	12.9	
		S. Typhosa	48	5	21	---	50 → 500	10.2	13.5	19.5	++
		E. Coli	48	5	20	---	100 → 700	9.1	15.7	21.3	+++
3	4/11/60	Control *	--	-	22	252	---	5.6	9.8	12.2	
		S. Typhosa	48	5	22	247	50 → 700	5.2	8.1	13.3	-
4	5/4/60	Control	--	-	22	266	---	6.4	10.0	12.6	
		E. Coli	48	5	27	269	100 → 700	6.3	8.3	10.0	-
		S. Typhosa	48	5	21	263	50 → 500	6.7	10.1	12.1	-
5	5/27/60	Control	--	-	18	266	---	7.1	9.7	14.4	
		E. Coli	48	10	19	269	100 → 1000	9.5	18.1	36.7	+++
		S. Typhosa	48	5	14	263	100 → 700	10.3	13.6	15.6	++
		Zymosan	24	2(I.V.) **	9	261	1 mg./100 gms.	11.9	15.7	19.5	+++
6	6/10/60	Control	--	-	24	264	---	7.5	11.3	16.3	
		E. Coli	48	10	17	250	100 → 1200	10.3	18.4	36.7	+++
		S. Aureus	48	10	16	241	100 → 1200	12.7	21.0	29.6	+++
		S. Typhosa	48	10	15	226	100 → 1200	12.7	25.0	46.7	+++
7	8/16/60	Control	--	-	19	320	---	6.9	8.5	9.5	
		S. Typhosa	48	10	15	286	100 → 1200	5.7	10.2	11.5	+
		S. Typhosa	72	10	15	281	100 → 1200	4.8	9.1	12.1	-
8	11/11/60	Control	--	-	19	249	---	5.2	11.1	21.6	
		S. Typhosa	48	10	25	246	100 → 1200	7.8	15.5	22.8	++

* Same Control as Experiment I.

** See Methods.

Except for Zymosan, all of the stimulating substances are endotoxins derived from bacteria. The $ST_{50\%}$ represents the median survival time, the best measure of the groups' performance as a whole. The results are evaluated in a semi-quantitative fashion: (-) is no statistically significant increase over control rats, (+) is a statistically significant increase of median survival of 1.5 to 3.0 min. over controls, (++) is an increase of 3.0 to 5.0 min., and (+++) is an increase greater than 5.0 min.

TABLE IV

SUMMARY AND EVALUATION OF DIFFERENT FACTORS IN THE EXPERIMENTS OF RATS WITH RETICULO-ENDOTHELIAL SYSTEM STIMULATION UNDERGOING 20 POSITIVE G ACCELERATION

Group	Groups compared	Group	Number in group	Average weight (gms.)	Survival times at % alive (min.)			Statistical difference* (5% level)
					$ST_{75\%}$	$ST_{50\%}$	$ST_{25\%}$	
I	All RES Stim. Rats and all Controls	Controls RES Stim.	148 280	269 257	7.5 8.3	9.9 11 5	13.7 19.4	+
II	RES Stim. Rats (5 injections) and their controls	Controls RES Stim.	86 147	261 259	7.6 7.9	10.0 10.7	13.3 15.5	-
III	RES Stim. Rats (10 injections) and their controls	Controls RES Stim.	80 122	274 244	7.1 8.8	9.7 14.2	13.3 25.8	+
IV	RES Stim. Rats with Low (to 500μ gms), Medium (to 700μ gms), and High (to 1200μ gms) doses of Endotoxin	Low Medium High	65 83 122	263 259 244	8.6 7.4 8.8	10.9 10.2 14.4	15.5 14.6 25.8	- +
V	RES Stim. Rats receiving different types of Endotoxin	E. Coli S. Aureus S. Typhosa	36 16 40	260 241 238	10.2 8.8 12.7	18.4 18.6 21.0	36.7 28.6 29.6	-
VI	Control rats of Successful and Unsuccessful Experiments	Successful Unsuccessful	63 85	260 269	7.8 6.9	11.3 9.3	13.0 16.7	+

* See Litchfield (16)

Summary of the survival to 20 positive G acceleration of all the RES stimulated rats and their controls and an evaluation of different variables determining prolongation of survival of the RES stimulated animals. The survival times are given for each group of rats at 75, 50 and 25% survival, but statistical analysis is limited to the 50% (median, $ST_{50\%}$) survival.

In Group IV, comparing low, medium and high doses of endotoxin, it must be noted that this groups all types of endotoxins at each dose, and that the "high" doses are administered in 10 injections, while the low and the medium doses are given in 5 injections. The low and medium dose groups do not differ significantly from each other but both differ significantly from the high dose group.

Analysis of Factors for Optimal RES Stimulation

This summary of all the experiments includes two experiments in which no enhancement of acceleration was obtained (Experiments 3 and 4) and one (Experiment 7) in which only slight enhancement was obtained. Thus the data were analyzed to see what factors are responsible for increasing the tolerance to a more significant degree. If the performance of the rats to which 5 injections were given are compared to their controls, (Group II of Table IV), the median survival is 10.0 min for 86 controls, and 10.7 min for 147 RES stimulated animals, an insignificant increase.

Because of these indifferent results, the next experiments employed 10 injections of endotoxin at higher doses. Comparing those rats receiving 10 injections of endotoxin with their controls (Group III, Table IV), it is seen that the median survival time is 9.7 min for 80 controls and 14.2 min for 122 RES stimulated animals, a mean increase of 47%. The 25% survival time is 25.8 min for the RES stimulated animals compared to a control value of 13.3 min, an even more marked difference. Figure 1 is the graph of the animals' survival compared with their controls, plotted on probit-log paper, showing the marked difference between the two populations.

The data were analyzed further for differences due to the dosage of endotoxin given. As shown in Group IV of Table IV, rats given endotoxin at doses up to 500 μgms (i.e., 50, 100, 200, 300, 500 μgms) have the same survival as those given endotoxin up to 700 gms (i.e., 100, 200, 300, 500, 700 μgms). However, those animals given endotoxin up to a final dose of 1200 μgms (100, 200, 300, 400, 500, 600, 800, 1000, 1200) have statistically significant increased survival compared to either of the other dose schedules; this was the schedule used in all of the later experiments. It must be emphasized that this higher amount was given in 10 injections, so it is impossible to say whether the effect was due to higher doses or more injections — probably both factors were responsible.

Finally, to see what effect different RES stimulating substances have on tolerance, the data were analyzed for differences as to the type of endotoxin utilized (Group V of Table IV). No significant difference was noted between the three endotoxins employed, Staphylococcus Aureus, Salmonella Typhosa, and Escherichia Coli.

Failure of RES Stimulation

It is seen in Figure 1 that those animals receiving 10 injections at high doses of endotoxin show a marked prolongation of survival to 20 positive G acceleration compared to control animals. However, with

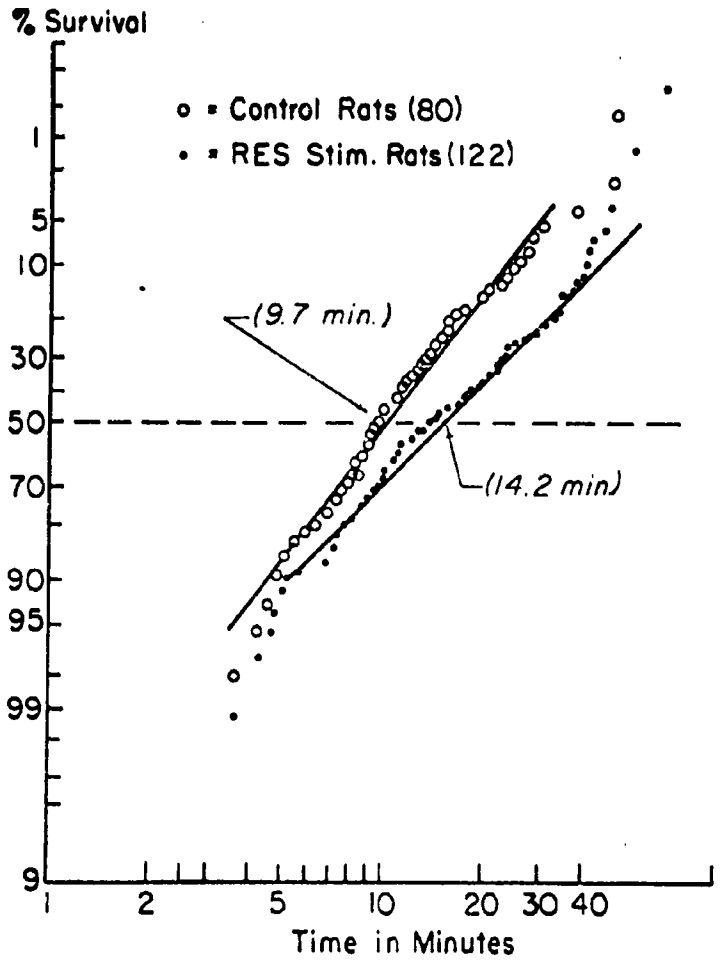

Figure 1. The effect of RES stimulation on survival to 20 positive G acceleration of all rats given 10 injections of endotoxin.

The vertical coordinate is a probit scale of percent survival and the horizontal coordinate is a logarithmic scale of time in minutes. The median survival time is indicated by the interception of the graphs with the 50% survival line.

certain animals in this group (Experiment 7 of Table III) despite 10 injections at high doses, only borderline results were achieved although 3 other experiments at this level were very successful. It was noted that it was possible to predict with good certainty if RES stimulation was going to be effective simply by observing the performance of the controls from the same group of rats. If the median survival of the controls was over 10.0 min and a fair percentage (10 to 30%) survived over 15 min, it was a certainty that RES stimulation would be effective. If, however, the controls had a median survival under 10.0 min and there were few or none that survived 15 min, RES stimulation was unsuccessful. To test this hypothesis, the controls from successful experiments were compared with those from unsuccessful experiments (Group VI of Table IV). The controls from unsuccessful experiments had a median survival time of 9.3 min compared to 11.3 min for controls from successful experiments, a statistically significant difference. The 25% survival times of the two groups are even more diverse, 13.0 min and 16.7 min for the two groups, successful and unsuccessful.

It can be concluded that if a population of rats had a fairly high initial resistance to acceleration, RES stimulation was effective. If for some reason the rats were more susceptible to acceleration, RES stimulation was not effective. Furthermore, when RES stimulation was effective, it increased survival to a greater extent in those animals with an already long survival since the differences of the 25% survival times are always more marked than differences of the 50% survival times in a successful experiment. It follows that RES stimulation effects primarily those animals that are normal or have good resistance to acceleration before any treatment.

If we consider the most resistant group of animals as judged by the survival of their control groups, the results of RES stimulation on acceleration tolerance is most evident (Figure 2). Here 48 RES stimulated rats have a median survival time of 23.6 min compared to a control value of 11.3 min, an increase of 112%; the 25% survival time is 40.0 min compared to the control value of 17.2 min. It must be emphasized that this is the best result obtained.

The fact that certain groups of animals have varying resistances to stresses is widely known. Some of this may be seasonal variation as noted in the rat's resistance to drum trauma (16) but more likely was due to the presence in the animal of respiratory disease, often subclinical (18) which would tend to produce RES blockade. This is plausible since the rats in Experiment 4, an unsuccessful experiment done in the Spring, had a high percentage of "runts", wheezing in the colony, and a few spontaneous

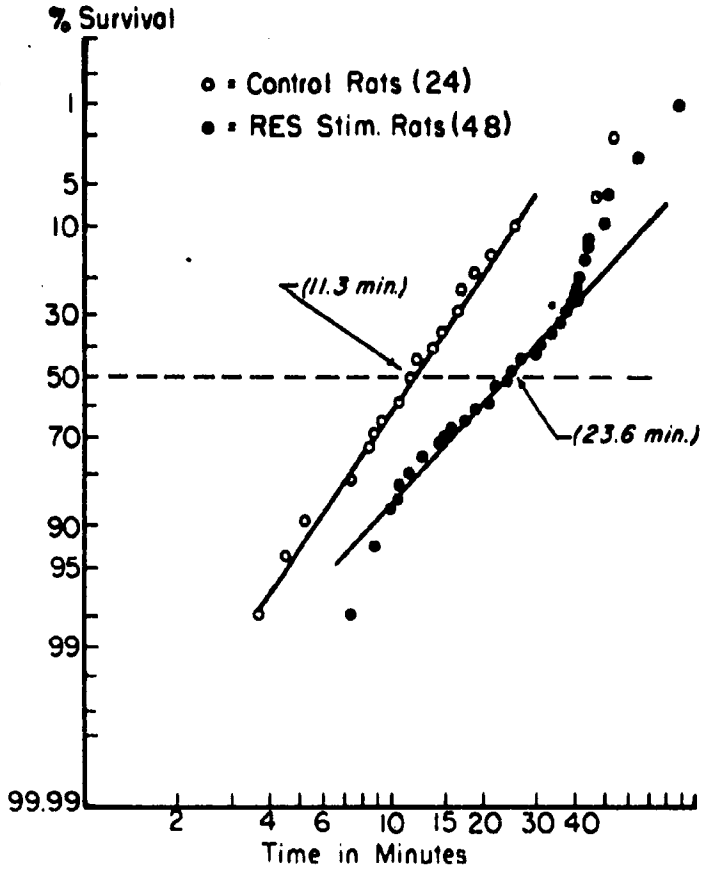

Figure 2. The effect of RES stimulation on survival to the 20 positive G acceleration of rats with some resistance to acceleration before stimulation (Expt. 6).

The vertical coordinate is a probit scale of percent survival and the horizontal coordinate is a logarithmic scale of time in minutes. The median survival time is indicated by the interception of the graphs with the 50% survival line.

deaths with pathologic evidence of pneumonitis. It was also noted that most of the rats' GI tracts were infested with Syphacia Obvelata nematodes, an endemic infection, that gradually increased in severity. Any of these factors could diminish the resistance of a particular rat population.

RES Blockade

To further delineate the role of the RES in acceleration protection, effect of inhibition or blockade of the RES on acceleration tolerance was investigated. The result of such an experiment is shown in Figure 3. After RES blockade, the median survival time of a group of rats at 20 G acceleration is about the same as that of a control group but the number of rats with prolonged survival was diminished. In a control group, 6 of 24 survived over 15 min, but in the blockaded groups, only 2 of 19 survived to 15 min. From these data it seems that RES blockade did not effect the acceleration tolerance of average rats, but did decrease tolerance in those having a prolonged survival time. These rats with blockaded RES then resemble very closely a group of controls from an "unsuccessful" experiment. Thus both stimulation and blockade can occur only in animals with normal or prolonged RES resistance. Furthermore, rats with diminished tolerance may have an RES already blockaded by infection, thus explaining their failure to respond to any type of RES stimulation.

DISCUSSION

The RES is intimately connected with an animal's ability to withstand stress. Hypertrophy of this system following administration of such substances as bacterial lipopolysaccharide (endotoxin) is associated with increased resistance to many stresses, and as shown in this paper, includes acceleration stress. Resistance to acceleration stress involves cardiovascular hemodynamics, anatomical compensations for displacement of viscera, and ultimately tolerance to cellular anoxia. Thus it has some of the characteristics of hemorrhage shock and drum trauma, both of which may be modified by RES stimulation.

It was shown that both RES stimulation and RES blockade effect the acceleration tolerance only of those rats with normal or prolonged resistance before any treatment. One might conclude that (1) RES blockade is dominant over RES stimulation, i.e., blockade will abolish a stimulated RES but stimulation is ineffective in a blockaded RES, (2) RES blockade usually results in average or diminished acceleration tolerance, (3) control groups of rats with prolonged acceleration tolerance may have an already stimulated RES, (4) control groups of rats which do not respond to RES already have RES blockade.

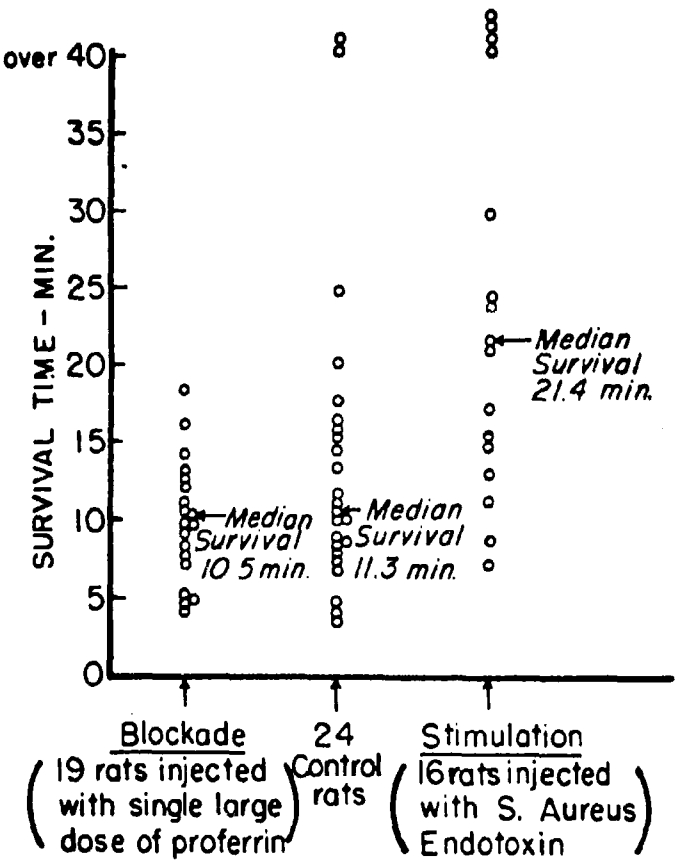

Figure 3. The effect of RES blockade on survival to 20 positive G acceleration.

The vertical coordinate represents the survival time. Each circle represents one animal. The median survival times are indicated by the arrows.

Mechanism of Action

Three methods have been found to be effective in enhancing acceleration tolerance, conditioning, hypophysectomy, and RES stimulation. Despite their superficial dissimilarities, there is some evidence that a common mechanism may be involved.

Conditioning regimes resemble RES stimulation. Cross conditioning occurs, i.e., conditioning against one stress protects against a different type (18) suggesting a "nonspecific" resistance to stress similar to that present in RES stimulation. Histologically, conditioning results in a state of RES hypertrophy and adrenal hypertrophy (20). Thirdly, RES blockade will abolish stress tolerance induced by conditioning (9).

Resistance to stress, and especially "natural resistance" as seen in RES stimulation and possibly conditioning is intimately associated with steroid metabolism (18). Steroids are very important regulators of cellular metabolism, specific alterations of which may result in resistance to acceleration. This is especially plausible since prolongation of acceleration tolerance by hypophysectomy seems likely to be achieved by alteration in steroid hormone regulation. The RES has a known effect on the metabolism of endogenous steroids (21), the functional state altering the metabolic destruction of different hormones; conversely steroids effect greatly the functional state of the RES; cortisone, for example, stimulates phagocytosis at low doses and inhibits at high doses (21). In addition, adrenalectomy results in a state where RES stimulation is difficult to induce, and blockade is facilitated (20).

It may well be possible that any increase in acceleration tolerance is mediated through the hypophyseal-adrenal axis. This is not a simple deficiency or excess of adrenal hormones, but is probably a specific humoral pattern. This pattern probably is approximated closely by hypophysectomy while adrenalectomy completely unbalances the hormonal interplay with a loss of acceleration tolerance. Conditioning alters the RES and the adrenals in a way that the specific hormonal pattern necessary for maximum acceleration tolerance is approached. Similarly, RES stimulation alone, through exhaustion or alteration of steroid metabolism, may achieve a similar pattern. This humoral pattern probably effects cellular metabolism in a manner that permits the hypoxia of acceleration to be more readily tolerated. As a possible mechanism for this, Polis (5) from studies on hypophysectomized animals, has suggested that energy demands for specialized functions and long term survival needs are decreased so that more energy can be channeled into elementary survival.

RES stimulation may increase resistance to acceleration by other means such as an increased detoxification of metabolic wastes, or by an increase in substances known to play a role in natural resistance such as complement, and properdin (23). These mechanisms are less well understood than hormonal alterations.

Use of RES Stimulation as a Practical Tool

Use of RES stimulation by means of endotoxin is safe from the standpoint of fatalities in animals. However, there are definite side effects of endotoxin such as hyperpyrexia, hypotension, and growth retardation (13). At present there is some effort being made to separate the RES stimulating portion of the lipopolysaccharides from the toxic portions. Heller (24) has partially purified a substance "RESTIM" from yeast which he feels is a very potent nontoxic stimulator. Until such substances are available, human studies must be deferred.

Utilization of nontoxic means to stimulate the RES system of humans is especially intriguing in space ventures. The increased natural resistance following RES stimulation would be expected to protect the subject against other stresses besides acceleration that would be encountered in space such as vibration and x-irradiation.

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