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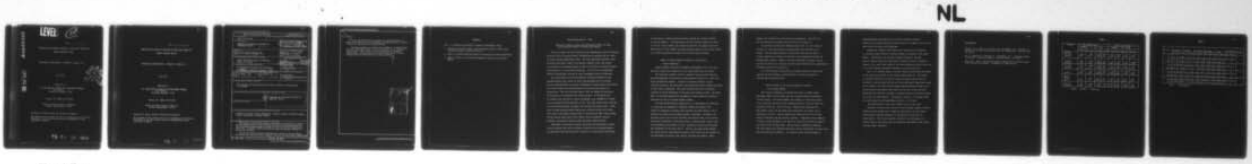

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ANNUAL PROGRESS REPORT

RESPONSIBLE INVESTIGATOR: RICHARD H. EGDAHL, M.D.

July 1978

Supported by

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

Hemorrhagic shock-induced insulin resistance and alterations in muscle leucine oxidation and protein synthesis occurred in pancreatectomized and adrenalectomized monkeys despite prevention of shock-induced alterations in pancreatic or adrenal hormone secretion through the constant infusion of insulin and cortisol.

Muscle and general protein metabolism were studied in rhesus monkeys postoperatively with and without adequate nutrition including amino (continued)

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20. acids.

It was concluded that the provision of adequate amounts of amino acids improves the post-traumatic nitrogen balance in primates probably by reducing muscle hypercatabolism.

Circadian rhythms for cortisol were studied in 5 monkeys before and after hemorrhagic shock. In only one animal was a circadian pattern seen in the control period, possibly due to technical difficulties. Interestingly, in the post-shock period 4 of the monkeys exhibited characteristic circadian rhythms.

CONTENTS

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Variation in Caloric Intake and the Metabolic Effect of Shock with Controlled Inputs of Cortisol and Insulin

Previous studies from this laboratory have demonstrated insulin resistance, elevated levels of glucocorticoids, epinepherine and glucagon and low levels of insulin allowing hemorrhagic shock. The most significant metabolic event occurring after major trauma is the general catabolic state that exists. If continued for an extended period of time or occurring in previously debilitated patients, it can be life threatening. If we are to give meaningful therapy the mechanisms involved in these derangements must be elucidated.

Ten rhesus monkeys were splenectomized, pancreatectomized (Ps) and adrenalectomized (Ax), placed in chairs and maintained with IV nutrient solution (80cal/kg/day) and constant replacement of hydrocortisone and insulin. Ten control monkeys were splenectomized only and received similar IV alimentation. One week following surgery, half the animals in each group were reduced to 24 cal/kg/day (low calorie group). On the eighth day, all monkeys were subjected to severe hemorrhagic shock (40mmHg for 3 hours) with a resulting five day mortality of 50%. The high calorie group continued to received 80 cal/kg/day throughout and following the shock period. Blood, urine and gastrocnemius muscle samples were collected before and 24 hours after shock to determine nitrogen balance (corrected for BUN), blood glucose, FFA and alanine levels and in vitro muscle leucine oxidation, protein synthesis, and glucose oxidation (with and without added insulin).

Hemorrhagic shock-induced insulin resistance and alterations in muscle leucine oxidation and protein synthesis occurred in the pancreatectomized and adrenalectomized groups despite prevention of shock-induced alterations

in pancreatic or adrenal hormone secretion through the constant infusion of insulin (Table 1). The suppression of muscle protein synthesis by shock in the low calorie animals was reversed by provision of adequate nutrition. Shock failed to alter further the large nitrogen losses of low calorie animals or to induce significant nitrogen loss in well alimented animals.

Effect of Altered Substrate Supply on Postoperative Protein Metabolism

Further studies involving the metabolic derangements that occur after shock and trauma were carried out in our rhesus monkey hind limb model.

The early post-traumatic period is marked by protein hypercatabolism and gluconeogenesis with negative nitrogen balance lasting 2 to 5 days after major uncomplicated surgery. In spite of important advances in post-operative nutrition, the potentially life-threatening protein wasting mechanism is still poorly understood. This study evaluates the role of substrate provision on muscle metabolism in the early post-traumatic period. An animal model is used which permits the assessment of muscle uptake and release of substrates as well as nitrogen balance studies.

Four male rhesus monkeys, weighing 8.1 to 15 kilograms, were submitted to laparotomy for placement of catheters through the internal iliac vessels for sampling of external iliac arterial and venous blood; a Foley catheter was placed in the bladder through a cystostomy. Throughout the procedure and for the 24 hours following the operation (Day 1) the animals, previously aclimatized to restraining chairs, received normal saline; this was followed by the provision of total parenteral nutrition with Freamine (80 cal/kg/day) for 24 hours (Day 2). Arterial and venous blood samples were drawn from the unanesthetized animals at the end of the two periods for the measurement of glucose, FFA, lactate, pyruvate and alanine. Urine

samples were collected for total nitrogen determination. The data for the two periods were compared using a paired t-test (Table 2).

In the 24-hour period that followed surgery (Day 1), a net output of alanine for muscle and negative nitrogen balance were observed in all animals. The nutritional support in the second 24-hour period (Day 2) produced significant reduction or reversal of both phenomena ($p<0.01$) and hyperglycemia ($p<0.01$). However, the muscle handling of glucose, lactate, pyruvate and FFA was not affected (arterio-venous differences not significantly different between Day 1 and Day 2).

It is concluded that the provision of adequate amounts of amino acids improves the post-traumatic nitrogen balance in primates probably by reducing muscle hypercatabolism

Effect of Shock on the Circadian Rhythm of Cortisol in the Rhesus Monkey.

This study was designed to determine the effect of medium volume hemorrhage (20% of blood volume) upon the circadian rhythm of peripheral cortisol levels. Five rhesus monkeys were adapted to restraining chairs in our isolation room with 12 hour light/dark cycles. Food and water were available ad libitum. After 7-10 days, catheters were implanted into both femoral veins, and the monkeys were returned to the chairs for an additional 7-10 days. Control samples were drawn each hour for 48 hours using a withdrawal pump and fraction collector. Immediately after sampling a volume of blood estimated to be 20% of the total blood volume was removed and stored at $4^{\circ}C$ in blood bags. Two days later, sampling was repeated. The blood samples were handled aseptically, and the resuspended red blood cells were reinfused during sampling. The cortisol levels were determined by

radioimmunoassay and subjected to non-linear regression analysis fitting of sine-cosine models which would reflect a circadian cycle and any phase shifts occurring after hemorrhage.

Significant technical difficulties were encountered in attempting to establish normal baseline circadian rhythms for hormones in the rhesus monkey. Specifically, our problems included swelling of the legs when the femoral veins were catheterized, potential effects of sampling because of the small blood volume of the rhesus monkey and lack of tight control of the temporal information received in the isolation room.

Only 1 of 5 monkeys showed a circadian rhythm by statistical non-linear cosine regression analysis in the control period (Table 3). The absence of circadian rhythms in the control period correlated closely with the incidence of leg swelling which may well have represented significant stress to the animals. The 48ml of blood removed during sampling (Ca 20%) of the blood volume of the animals under study also may have caused sufficient hemodynamic and metabolic responses to further obscure the circadian rhythm of cortisol in these animals. Interestingly, however, a circadian rhythm was found during the post-hemorrhage period in 4 of 5 cases

The significance of this latter finding is not at all clear.

Although, as stated, this initial work on circadian rhythms in rhesus monkeys has been fraught with a number of difficulties, we have gained much valuable technical experience in the approach to this area of investigation. This we have already utilized in the development of a similar model in the baboon which in preliminary experiments shows promise of being highly successful.

PUBLICATIONS

Whitten, R. H., Ryan, N.T., George, B.C. and Egdahl, R.H.: The Role of adrenal and pancreatic hormones in post shock metabolism. Surgical Forum. (in press).

Aun, F., Meguid, M., Albertson, D., and Egdahl, R.H.: Circadian Rhythms of cortisol: Effects of Surgery. Surgical Forum. (in press).

Ryan, N.T.: Role of the Adrenal Glands in Metabolism of Skeletal Muscle from Streptozoticin monkeys. (Submitted for publication).

TABLE 1

RESULTS:	LOW CALORIE GROUP				HIGH CALORIE GROUP			
	CONTROL		Px Ax		CONTROL		Px Ax	
	Preshk	Postshk	Preshk	Postshk	Preshk	Postshk	Preshk	Postshk
MUSCLE Leu Oxid um/gm/hr	.020 ±.005	.029* ±.004	.0193 ±.006	.023* ±.010	.015 ±.001	.036* ±.009	.020 ±.007	.032* ±.002
Leu-Prot um/gm/hr	.065 ±.018	.037* ±.003	.036 ±.006	.025 ±.009	.033 ±.001	.047* ±.009	.019 ±.007	.080** ±.002
Glu Oxid um/gm/hr	.227 ±.041	.205* ±.021	.181 ±.014	.178 ±.059	.174 ±.020	.241* ±.030	.212 ±.060	.171 ±.023
+ Insulin	.374* ±.047	.236 ±.024	.411* ±.049	.202 ±.079	.375* ±.050	.208 ±.020	.335* ±.059	.198 ±.056
BLOOD Alanine um/cc	.43 ±.09	.65* ±.15	1.49 ±.06	1.94* ±.32	.255 ±.02	.285 ±.03	1.68 ±.22	2.02* ±.26
Nit Bal gm/kg/day	-.422 ±.064	-.438 ±.081	-.502 ±.032	-.436 ±.112	±.072 ±.077	±.062 ±.052	-.026 ±.076	-.027 ±.045

(±SEM) (*$p<0.5$) (**$p<0.01$)

TABLE 2

Animal #		GLUCOSE*		LACTATE*		PYRUVATE*		ALANINE*		FFA*		N BALANCE**		B-MH
		Day 1	Day 2	Day 1	Day2	Day 1	Day 2	Day 1	Day 2	Day 1	Day 2	Day 1	Day2	
1	A	6.25	22.05	13.0	15.0	.213	.153	.772	1.352	.874	2.84	-303	±296	
	A-V	-8.5	-7.05	-2.56	-5.7	-.041	-.045	-.558	-.226	-.018	±.84			
2	A	6.6	16.98	1.54	0.70	.055	.075	.289	.200	.946	.910	-209	± 65	
	A-V	±0.4	-.21	±.21	-.80	0	-.024	-.177	-.265	-.005	-.027			
3	A	5.8	26.49	0.91	1.02	.232	.367	.142	.133	.843	.756	-167	±139	
	A-V	±1.05	- .22	-.28	-1.15	-.126	±.037	-106	±.026	-.146	±.108			
4	A	5.8	12.75	3.75	1.02	.215	.202	.383	.238	.874	.205	-635	-458	
	A-V	±1.05	±1.40	±1.2	-1.15	±0.54	±.058	-.133	-.067	-.017	-.014			

*mM/L *mg N/Kg/day

TABLE 3

Animal	Coefficient of Determination* R^2 (%) Pre	Post	Phase Angle (95% Confidence) Interval Pre	Post
1	83**	66**	0.8 (.6, 1.01)	1.55 (1.23, 1.86)
2	7	58**		
3	15	75**		
4	4	6		
5	7	48**		

*Suggestive of circadian rhythm.

**Coefficient of Determination due to fitting the data to a cosine function.

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