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SELECTED REPORTS AND NOTES

Modification of Lethality Induced by Staphylococcal Enterotoxin B in Dutch Rabbits

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SUMMARY

Intramuscular injection of staphylococcal enterotoxin B (SEB) at a dosage level of 50 μg/kg of body weight caused death in Dutch rabbits. Lethality was not modified markedly by morphine pretreatment or by hyperthermia, thyrotoxicosis, propylthiouracil feeding, thyroparathyroidectomy, water deprivation, or fasting. The administration of acetylsalicylic acid to the SEB-inoculated rabbit also failed to protect the rabbits from the effect of SEB. Seemingly, the SEB molecular destruction was not markedly modified by alteration of cellular metabolism, and lethal effects of SEB remained unchanged in the morphine- or acetylsalicylic acid-treated rabbits.

When SEB was given to six rabbits 3 days after total-body X-irradiation, fever persisted and three rabbits survived. An identical dose of SEB to nonirradiated rabbits produced fever initially, followed by hypothermia and death of all six rabbits.

A single IV injection of a small quantity of purified staphylococcal enterotoxin B (SEB) has been shown to produce death within 24 hours in monkeys,[1-3] dogs,[4,5] and rabbits.[6-7] Although an enteric endotoxin release was suggested as the cause of death in rabbits,[7] reduction of body fluid volume, blood pooling in the peripheral capillaries,[3,8] pulmonary edema,[9,10] and activation of the kinin system[11] were considered to be associated with SEB toxemia and death in rhesus macaques. How to modify SEB toxicity in the monkey and rabbit is still of much interest to scientists searching for information to develop means of treating SEB toxemia.

Staphylococcal enterotoxin B is a single polypeptide chain with a molecular weight of 35,300.[12] Warren et al[13] proposed that the closed disulfide loop of SEB is related to stabilization of its native chemical structure. The complete amino acid structure of the SEB molecule was reviewed and summarized by Beisel.[14] Because a major portion of the IV-injected dose of labeled SEB accumulates in the renal proximal tubule,[15,16] the kidney[17] has been sug-

TABLE 1—Allocation of 84 Dutch Rabbits into 6 Groups and 12 Subgroups for Studying Modifications of Staphylococcal Enterotoxin B (SEB) Toxemia

Group	(n)	Treatment	Days prior to SEB (100 μg/kg of body weight)
I-Control*			
Ia	(4)	Rectal temperature = 38 to 39 C	ND
Ib	(6)	0.5 ml of 0.02 *N* NaOH/rabbit/day	6
Ic	(6)	None	ND
Id	(6)	None	ND
Ie	(5)	SEB (50 μg/kg), IM	NA
If	(6)	None	ND
II-Hypermetabolic			
IIa Hyperthermia	(4)	Rectal temperature = 40 to 40.5 C	0.5
IIb Thyroxine treated	(6)	2 mg/rabbit/day	6
III-Hypometabolic			
IIIa PTU treated	(5)	25 mg/rabbit/day	70
IIIb Thyroparathyroidectomized	(6)	Surgically removed	4
IIIc H_2O deprived	(6)	Without water	4
IIId Fasted	(6)	Without food	4
IV-Morphine treated	(6)	3 mg/rabbit/6 hours	3
V-Acetylsalicylic acid treated	(6)	217 mg/rabbit/6 hours for 48 hours, begun 15 minutes after SEB (50 μg/kg)	NA
VI-X-irradiated	(6)	500 R total-body exposure	3

* Corresponding control vs experimental groups = Ia vs IIa; Ib vs IIb; Ic vs IIIa; Id vs IIIb, IIIc, IIId, and IV; Ie vs V; If vs VI.

PTU = propylthiouracil; NA = not applicable; (n) = number. ND = not done.

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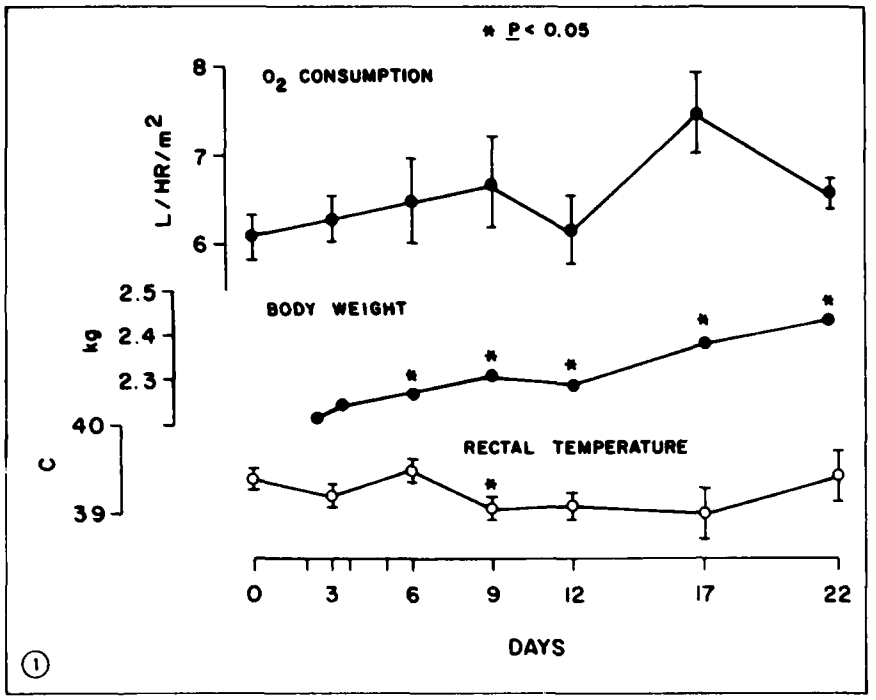

Fig 1—Changes in O_2 consumption, body weight, and rectal temperature of control rabbits (n = 6; group Ic). Time = 22 days.

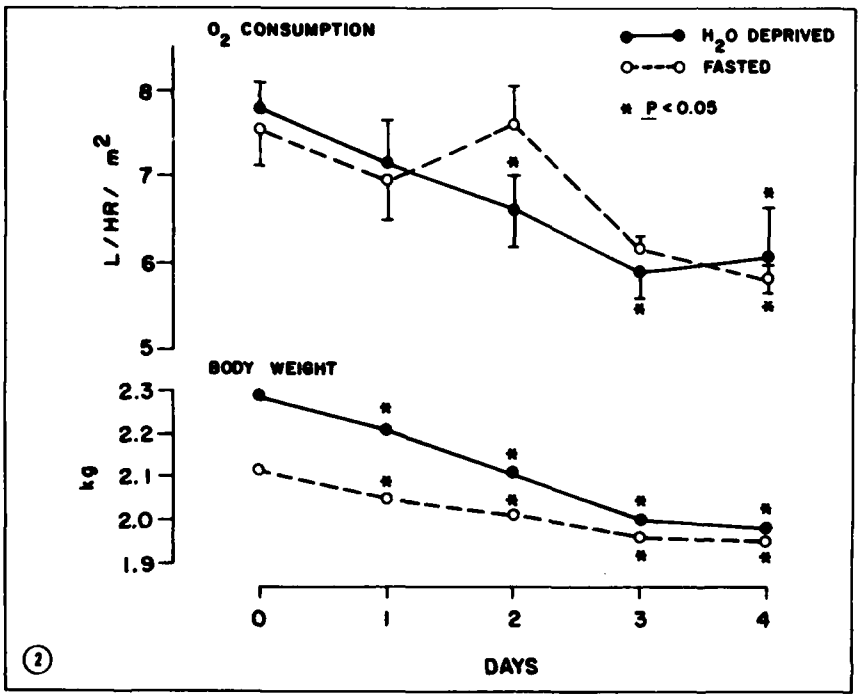

Fig 2—Effects of water deprivation and fasting on O_2 consumption and body weight of rabbits (n = 6/group; groups IIIc and IIId).

gested as the site for SEB catabolism in vivo. Results from in vitro studies[18,19] indicate that lysosomal protease might be responsible for SEB catabolism. However, Canonico et al[20] suggested that SEB was first pinocytized by renal tubular cells and subsequently was sequestered within vesicles having physical and biochemical properties of lysosomes.

Treatment of monkeys[21] or rabbits[22] with a single total-body X-irradiation (400 to 500 R) 4 days prior to lethal doses of SEB inoculation prolonged survival. The exact mechanism for the modification of SEB toxicity is not known. Because O_2 consumption decreased markedly after a nonlethal total-body X-ray exposure (500 R) in rabbits,[22] the present study was designed to test the hypothesis that experimentally induced hypometabolism (propylthiouracil, thyroparathyroidectomy, water deprivation, and fasting) or hypermetabolism (hyperthermia and thyroxine) would modify SEB toxicity and alter lethality. Other purposes of this study were: (1) to investigate the usefulness of morphine as a sedative[23] for alleviation of pulmonary edema,[24,25] and (2) to see if acetylsalicylic acid would inhibit synthesis of prostaglandins,[26] which might have a major role in causing death[27,28] in the SEB-inoculated rabbits.

Materials and Methods

Male Dutch rabbits (n = 84; *Oryctolagus cuniculus*), weighing 1.8 to 2.2 kg, were placed in six experimental groups (Table 1). Groups I, II, and III were further allocated among 12 subgroups, of which six subgroups were used as controls. Several different experimental conditions with various durations were induced prior to a single IM inoculation of highly purified SEB[29] (0.1 mg/kg). Acetylsalicylic acid (217 mg/rabbit) was given orally 15 minutes after IM injection of 50 μg of SEB/kg and was continued every 6 hours for 2 days (group V). All measurements were made in the same period under the same experimental conditions for control and corresponding treatment groups of rabbits.

Induction of Hypermetabolism—Hyperthermia (group IIa) was induced by placing conscious rabbits into a modified ventilated incubator with an internal temperature of 34 C for 12 hours until the rectal temperature of the rabbits reached 40 to 40.5 C. Rectal temperature was measured with a probe, and values were read on a telethermometer.[a] L-Thyroxine[b] was dissolved in 0.02 *N* NaOH[30] (4 mg/ml); a daily dose of thyroxine (2 mg/rabbit/day in a 0.5 ml volume) was administered subcutaneously (sc) for 6 days (group IIb). The corresponding controls (group Ib) were given the same volume of 0.02 *N* NaOH without L-thyroxine, SC.

Induction of Hypometabolism—Induction of various types of hypometabo-

[a] Yellow Springs Instrument Co, Yellow Springs, Ohio.

[b] Sigma Chemical Co, St Louis, Mo.

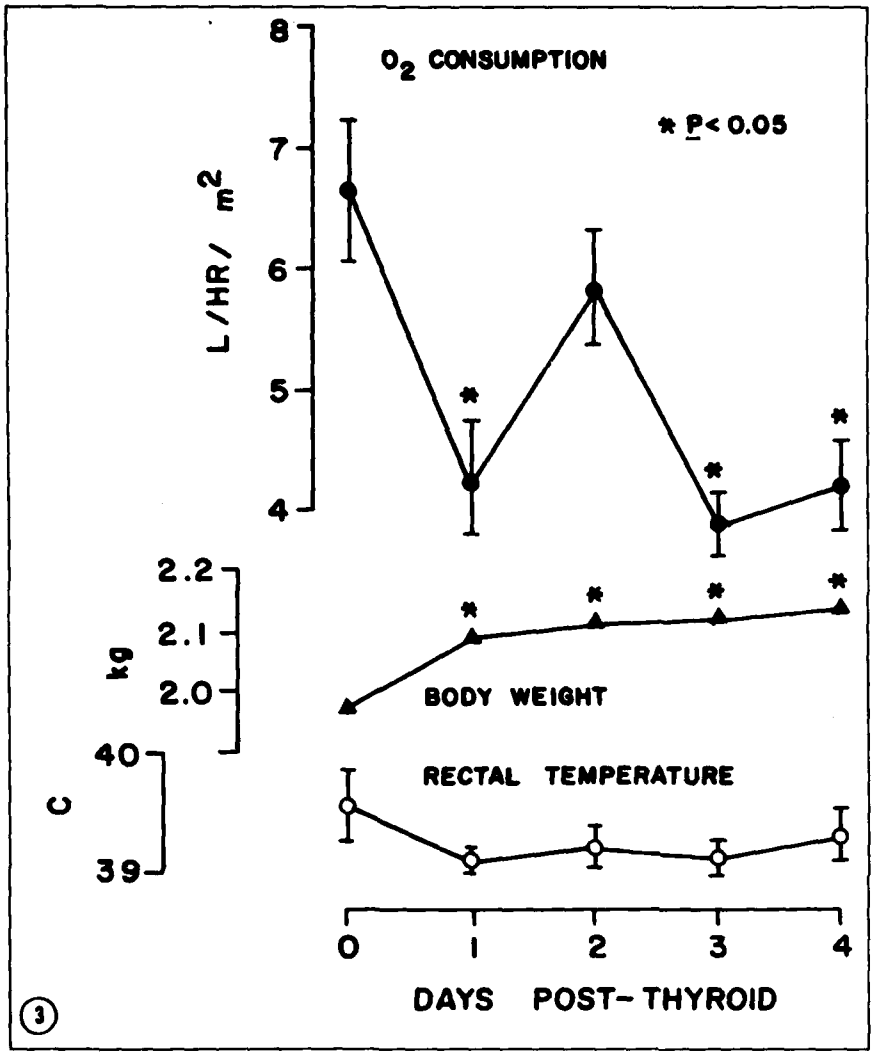

Fig 3—Effect of thyroparathyroidectomy (postthyroid) on O_2 consumption, body weight, and rectal temperature of rabbits (n = 6; group IIIb).

lism was attempted. Hypometabolism was induced by thyroparathyroidectomy (group IIIb), water deprivation (group IIIc), or fasting (group IIId) for 4 days prior to SEB inoculation (0.1 mg/kg, IM). Also, a group of rabbits was fed propylthiouracil (PTU; group IIIa) for 70 days and then were inoculated IM with SEB (0.1 mg/kg). The dose of PTU was 25 mg/rabbit/day; the suspension was given orally through a nasogastric tube, or the tubing was inserted directly into the stomach via the mouth. In the latter case, a metal mouth opener was used to prevent biting.

Morphinization of Rabbits—Six rabbits were given morphine SC (3 mg/rabbit) every 6 hours for 3 days (group IV), and then a single IM dose of 100 μg of SEB/kg was given.

Total-body O_2 consumption of the rabbit was measured with a 1-L spirometer.[c] The rabbit was restrained in a plastic box during the measurement of O_2 consumption for at least 15 minutes' conditioning and 9 minutes' actual recording. The measured volume of O_2 consumption was corrected with standard atmospheric pressure, temperature, and vapor pressure according to the gas law.

Total-Body X-Irradiation—The radiation exposure (500 R) was delivered from a 1-meV, 3-mA X-ray-generating unit[d] operating at an effective energy of 475 kiloelectron volt without added filtration. Before irradiation, each rabbit was anesthetized with droperidol and fentanyl[e] (0.15 ml/kg, IM) and was placed in a plastic acrylic resin cylinder (length, 49.5 cm; diameter, 13.6 cm), which was rotated at 1 rpm in the X-ray beam. The midline exposure rate was 30 R/minute in air at a distance of 118 cm.

A lethal dose of SEB (0.1 mg/kg) was injected IM into nonirradiated (group If) and irradiated (group VI) rabbits.

Recorded Data—The lethality or survival time was recorded for all groups of rabbits studied. Body weight, O_2 consumption, and rectal temperature were measured only in the L-thyroxine-treated, PTU-treated, thyroparathyroidectomized, water-deprived and fasted rabbits, and in their corresponding control groups.

Rectal temperatures were measured with a probe and telethermometer before and after SEB inoculation at various time intervals for a period of 20 hours; deaths were recorded.

Results

Effects of Water Deprivation, Fasting, Thyroparathyroidectomy, or PTU—Typical changes in O_2 consumption, body weight, and rectal temperature for 22 days in normal control Dutch rabbits are illustrated (Fig 1). A steady increase in body weights, with few changes in O_2 consumption and rectal temperature, was shown. However, O_2 consumption and body weights were significantly ($P < 0.05$) decreased 4 days after water deprivation or fasting, as compared with base-line values for the controls (Fig 2). After thyroparathyroidectomy, body weight increased markedly, and O_2 consumption was decreased without change in rectal temperature (Fig 3). Although body weight increased markedly between 8 and 10 weeks after an initial inhibition of growth in the PTU-treated rabbits, O_2 consumption and rectal temperature did not show marked changes during a 10-week PTU-feeding period (Fig 4).

Effects of L-Thyroxine—Effects of L-thyroxine on body weight and rectal temperature in rabbits are illustrated (Fig 5). Within 6 days, body weights of L-thyroxine-injected rabbits sharply decreased, whereas the

TABLE 2—Effect of Hyperthermia on SEB-Inoculated (0.1 mg/kg) Rabbits

Group	Hyperthermia 12 hours before SEB	Hyperthermia 4 hours after SEB
Control (Ia) (Room temperature)	4/4	3/4
Hyperthermia (IIa) (40.0–40.5 C)	4/4	4/4

Numerator = No. of deaths; denominator = No. of rabbits exposed.

[c] Warren E. Collins Inc, Braintree, Mass.

[d] General Electric Co, Milwaukee, Wis.

[e] Innovar-Vet, Pitman-Moore Inc, Washington Crossing, NJ.

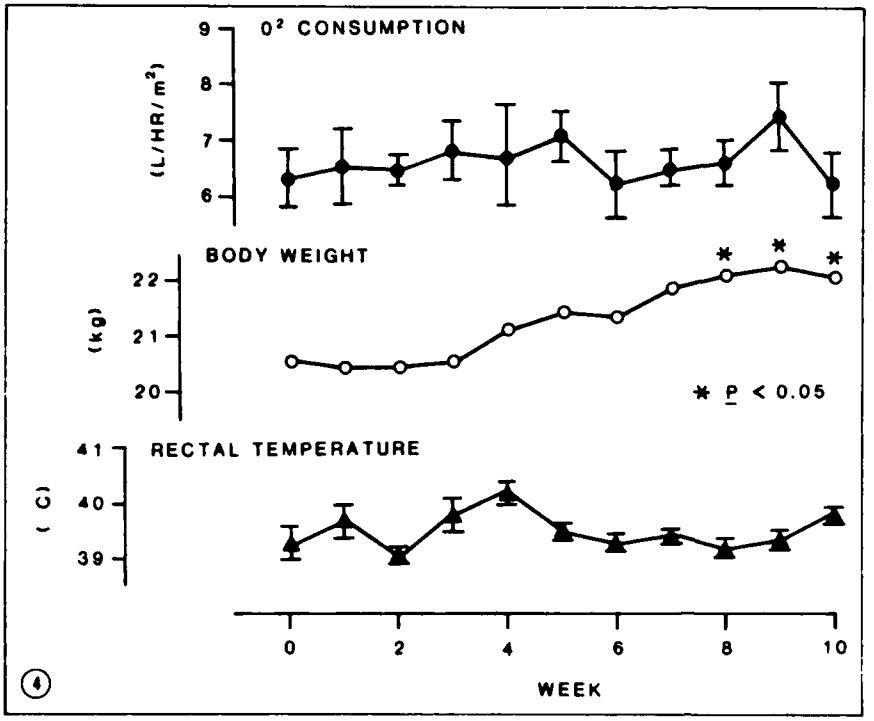

Fig 4—Effect of oral propylthiouracil (25 mg/day) on O_2 consumption, rectal temperature, and body weight in rabbits (n = 5; group IIIa) for 10 weeks.

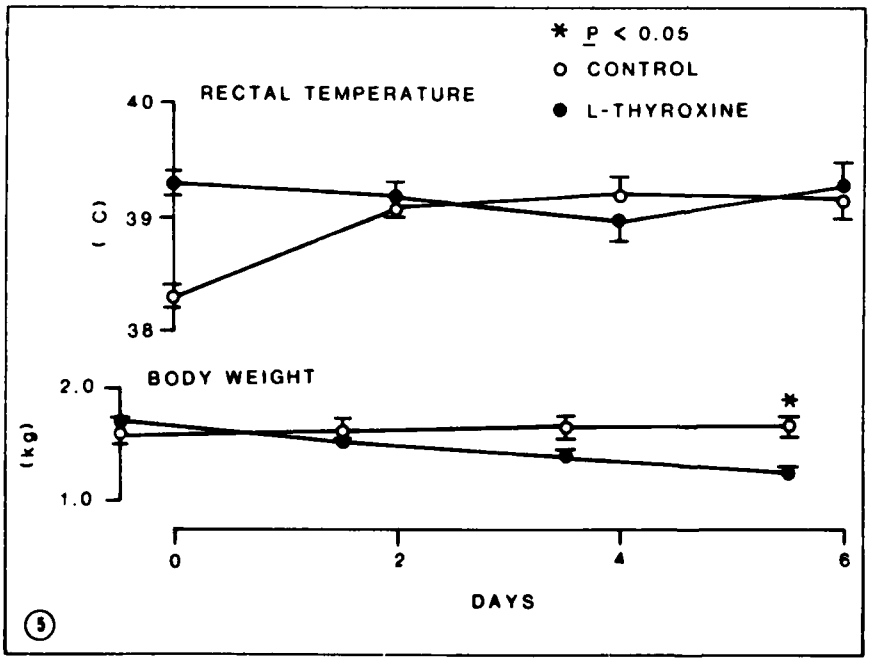

Fig 5—Changes in body weight and rectal temperature of control and L-thyroxine-treated rabbits (group IIb).

control group showed a slight increase in body weight. The rectal temperatures among control and L-thyroxine-treated rabbits were not significantly different ($P > 0.05$).

Effects of SEB in Hypermetabolic Rabbits—The effect of hyperthermia and L-thyroxine administration on SEB-exposed rabbits is summarized (Tables 2 and 3). Whether hyperthermia was applied before or after SEB, the number of deaths was essentially the same as compared with the number of deaths of controls (Table 2). Although all rabbits in the thyroxine-treated group died, control rabbits, which were given 0.5 ml of 0.02 *N* NaOH/day for 6 days, survived. The failure of these control animals to respond in the same way as did the other controls is not explained and is presumed to have occurred fortuitously.

Effects of SEB in Hypometabolic, Morphinized, and PTU-Treated Rabbits—Effects of SEB (0.1 mg/kg) on survival in hypometabolic (induced by thyroparathyroidectomy, water deprivation, and fasting) and morphinized rabbits are summarized (Tables 4 and 5). Significant difference was not observed in survival between control groups and each of the corresponding experimental groups.

Effects of SEB in X-Irradiated Rabbits—Changes in rectal temperature of irradiated and nonirradiated rabbits given SEB (100 μg/kg) 3 days after irradiation are illustrated (Fig 6). Fever was observed within 2 hours after SEB inoculation in both groups and persisted in the irradiated rabbits; decreased rectal temperatures below base-line values were found in nonirradiated rabbits. Although there was a trend for the rectal temperature to reach preinoculation values between 8 and 10 hours after SEB, all six nonirradiated rabbits died within 10 hours. However, three of six irradiated rabbits survived 20 hours after the SEB injection.

Discussion

The cause of SEB-induced death in rabbits has been attributed to endotoxin release from the intestine.[7] Pulmonary edema has been shown to be an important factor leading to death during SEB toxemia in rhesus macaques.[10] Further, Pettit et al[11] reported that the kinin system was activated in monkeys after a lethal IV dose of SEB. In the present study, acetylsalicylic acid failed to modify survival time after IM inoculation of SEB in rabbits, suggesting that prostaglandins may not be directly involved in the pathogenesis of shock and death.

Propylthiouracil is an antithyroid drug which decreases the formation of thyroid hormones by preventing iodi-

TABLE 3—Effect of Hypermetabolism (Induced by L-Thyroxine) on SEB Challenge-Exposed (0.1 mg/kg) Rabbits (Groups Ib and IIb)

Variable	Ib (controls; n = 6)		IIb (thyroxine treated; n = 6)	
	Day 0	Day 6	Day 0	Day 6
Rectal temperature (C)	38.8 ± 0.1	39.2 ± 0.2	39.3 ± 0.1	39.3 ± 0.2
O_2 consumption (L/hours/m^2)	7.0 ± 0.5	9.3 ± 1.0	7.8 ± 0.2	14.2 ± 0.3*
Body weight (kg)	1.59 ± 1.10	1.62 ± 0.09	1.67 ± 0.06	1.25 ± 0.05*
Survival after SEB on day 6 (%)		100		0*

* $P < 0.05$ vs controls.

Controls were given 0.5 ml of 0.02 *N* NaOH/day for 6 days. Thyroxine dosage = 2 mg/rabbit/day sc, in 0.5 ml of 0.02 *N* NaOH. n = No. of rabbits.

TABLE 4—Effects of Hypometabolism on SEB Challenge-Exposed (0.1 mg/kg) Rabbits (6/group)

Treatment	O_2 consumption (L/hour/m^2)		SEB given after procedures (days)	Survival time* (hours)	Survival (%)
	Prior to treatment	Prior to SEB			
Control	6.08 ± 0.26	6.53 ± 0.16	ND	15 ± 3.4	17
Thyroparathyroidectomized	6.64 ± 0.56	4.24 ± 0.31	4	20.6 ± 3.4	33
H_2O deprived	7.84 ± 0.42	6.07 ± 0.49	4	12.3 ± 2.0	0
Fasting	7.68 ± 0.69	5.83 ± 0.16	4	62 ± 47.1	50

* Refers only to rabbits that died.

ND = not done.

TABLE 5—Effects of SEB (0.1 mg/kg) on Survival of Rabbits Given Morphine or Propylthiouracil

Treatment (n)	O_2 consumption (L/hour/m^2)		Days after medication	Time to death* (hours)	Survival (%)
	Prior to treatment	Prior to SEB			
Control (6)	6.08 ± 0.26	6.53 ± 0.16	ND	19.4 ± 3.1	17
Morphine (5)	ND	ND	3	11.3 ± 1.25	20
PTU (5)	6.32 ± 0.43	6.21 ± 0.59	70	15.5 ± 2.5	0

* Only for rabbits that died.

ND = not done; PTU = propylthiouracil.

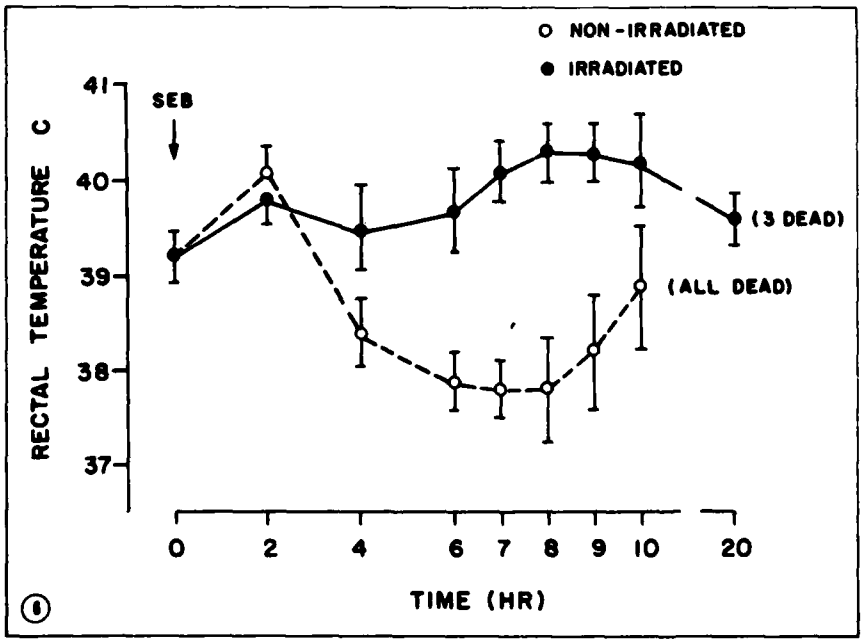

Fig 6—Changes in rectal temperature of total-body X-irradiated and nonirradiated rabbits given staphylococcal enterotoxin B (100 μg/kg) 3 days after irradiation (n = 6/group; group If and VI).

nation of tyrosine.[31] In the present study, daily oral feeding of PTU for a period of 70 days did not alter O_2 consumption and rectal temperature in Dutch rabbits. Only the body growth rate was inhibited during the first 3 weeks after initiation of PTU feeding. Because few changes occurred in the PTU-treated rabbits, it was not surprising to observe that PTU (25 mg/day) failed to modify SEB toxemia in rabbits with the dose schedule used.

If pulmonary edema is the main cause of death in SEB-intoxicated rabbits, pretreatment with morphine for 4 days might exert some beneficial effects by the sedative action and decrease in cardiac load.[23,24] According to our recent findings,[f] pulmonary edema did not occur at death of SEB-inoculated rabbits. Furthermore, Pettit et al[7] showed that endotoxemia was induced after SEB injection IV. This may explain why morphine did not have any protective action against lethal SEB toxemia in Dutch rabbits.

Experimentally induced hypermetabolism, including hyperthermia and pretreatment with L-thyroxine, did not alter SEB lethality in rabbits. These results indicate that SEB molecules are not easily catabolized or detoxified in the body, even with increased cellular metabolism. The findings that hypometabolism failed to prolong survival during SEB toxemia suggested that a decrease in O_2 consumption alone after 500 R of total-body X-irradiation[22] was not the key factor for survival in Dutch rabbits after an IM inoculation of SEB.

Rapoport et al[32] demonstrated that the administration of antiserum to SEB in rhesus macaques prevented a rapid disappearance of IV-injected SEB from the circulation. However, Beisel[8] pointed out that if macaques were hyperimmunized by repeated IV injections of an SEB antigen, typical anaphylactic reactions developed. Liu et al[21,g] reported that pretreatment with 400 R of total-body X-irradiation and continuous positive pressure were beneficial to rhesus macaques after an IV inoculation of SEB. Recently, a system of hemoperfusion through an activated charcoal column has been developed by Liu and Sanders.[h] The adsorptive capacity of activated charcoal to SEB in vitro and in rhesus macaques has also been shown.

Prevention of SEB-induced death by pretreatment with total-body X-irradiation (500 R) has been shown in the present study and in previous studies.[22] Mechanisms of survival appeared to be correlated with the abil-

[f] Unpublished data, 1977.

[g] Liu CT, DeLauter RD, Griffin MJ: Pulmonary dysfunction in rhesus monkeys during staphylococcal B enterotoxemia (abstr). *Physiologist* 19:273, 1976.

[h] Liu CT, Sanders RP: Development of a hemoperfusion system with activated charcoal for rhesus monkeys (abstr). *Fed Proc* 38:538, 1979.

ity to maintain fever after IM injection of SEB. Sustained fever after SEB challenge exposure may imply that SEB-induced fever in the irradiated host may originate centrally due to modification of hypothalamus functions. One of the possible reasons for survival with pretreatment of X-irradiation may be a result of sustained fever, because fever has been demonstrated to increase survival in the lizard and other animal models.[33-35] However, experimentally induced hyperthermia, by increasing rectal temperature 1 C, had no effect on survival during SEB toxemia in Dutch rabbits.

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