Page[13] has recently reported an increase in the membrane potential of cat heart muscle immersed in Ringer's fluid following the addition of bovine serum.

It is concluded from these results that with mammalian muscle (as already demonstrated with amphibian muscle) the resting membrane potential measured in plasma is in very good agreement with that calculated from the Nernst equation, indicating that the potential in the balanced state corresponds to the potassium equilibrium potential.

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[1] Kernan, R. P., and Conway, E. J., *Abstr. Intern. Congr. Biochem.* (1955).
[2] Harris, E. J., and Martins-Ferreira, H., *J. Exp. Biol.*, **32**, 539 (1955).
[3] Adrian, R. A., *J. Physiol.*, **133**, 631 (1956).
[4] Hodgkin, A. L., and Horowicz, P., *J. Physiol.*, **148**, 127 (1959).
[5] Graham, J., and Gerard, R. W., *J. Cell Comp. Physiol.*, **29**, 99 (1946).
[6] Conway, E. J., Twenty-first Congr. Intern. de Ciencias Fisiol., Buenos Aires (1959).
[7] Vaughan-Williams, E. M., *J. Physiol.*, **146**, 411 (1959).
[8] Pillat, B., Kraupp, O., Giebisch, G., and Stormann, H., *Pflügers Archiv. Ges. Physiol.*, **266**, 459 (1957).
[9] Kernan, R. P., *Nature*, **185**, 471 (1960).
[10] Carey, M. J., and Conway, E. J., *J. Physiol.*, **125**, 232 (1954).
[11] Creese, R., D'Silva, J. L., and Northover, J., *J. Physiol.*, **143**, 22P (1958).
[12] Conway, E. J., and Hingerty, D., *Biochem. J.*, **40**, 561 (1946).
[13] Page, E., *J. Gen. Physiol.*, **46**, 189 (1962).

Canine Endotoxin Shock: Protection against a Lethal Dose of Endotoxin following an Infusion of Histamine

WHEN a lethal dose of endotoxin is injected intravenously into adult mongrel dogs a decline in systemic blood pressure occurs within 1 min, reaching a maximum in 5–15 min, following which irreversible shock occurs. Work in this laboratory[1,2] and that of others[3–5] on endotoxin shock supports the concept that the initial hæmodynamic alterations in dogs, rabbits and monkeys involve an antigen–antibody reaction of the anaphylactic type with the prompt reduction of complement and the appearance of increased concentrations of vasoactive substances in the blood, including histamine.

We have confirmed our earlier observations in which a majority of animals were protected against a lethal dose of endotoxin when pre-treated with epsilon-aminocaproic acid (EACA) or cortisol[6,7]. However, as in control animals a decline in the hæmolytic activity of complement reached a maximum in 10 min after the injection of endotoxin, and then there was a rapid restoration of the pre-endotoxin-levels in the animals that recovered. In all groups of animals the rise in histamine usually reached a maximum within 60 sec, which coincided with the decline in blood-pressure. A fluorometric method for histamine assays was used[8]. The results in this communication originated in observations carried out in 10 dogs which had survived a lethal dose of endotoxin after pre-treatment, including EACA or cortisol. After an elapse of several days to many weeks a second lethal dose of endotoxin was given to each of these animals. This resulted immediately in a violent anaphylactic-like reaction with a marked decline in blood-pressure; decrease in complement; and the concentrations of histamine were among the highest observed in any groups of dogs studied. Seven of the 10 dogs survived. The unusually increased amounts of blood-histamine in dogs, a majority of which survived, suggested the following experiment in which dogs were pre-treated with histamine and then given a lethal dose of endotoxin.

Ten control adult animals, anæsthetized with 'Nembutal', were given 0·55 mg/kg endotoxin. None of these animals survived, as seen in Table 1. Ten dogs were each given an intravenous infusion of 1 mg of histamine phosphate base in 100 ml. of 5 per cent dextrose and water over a period of 15–20 min. The histamine did cause a decline in systemic pressure, similar to that induced by endotoxin; but the depression of urine flow was less severe. Approximately 15–20 min after the infusion of histamine had been completed, the arterial pressure had become stabilized at pre-histamine-levels and 0·55 mg of endotoxin was then injected. The resulting shock was less severe than in the control animals, and 8 out of 10 of the histamine-prepared animals survived (Table 1). This degree of protection was similar to that obtained by pre-treating animals with cortisol or with EACA. Investigations with control animals revealed that the anæsthesia did not alter the concentrations of histamine, nor did an infusion of 100 ml. of 5 per cent dextrose and water have an effect on the blood-histamine concentrations or protect against endotoxin. It is of interest that others[9] have recorded an increase in survival rates of mice against endotoxin by pre-treatment with histamine.

Table 1. EFFECT OF LETHAL DOSE OF ENDOTOXIN (0·55 MG/KG) IN CONTROL GROUP OF ADULT DOGS AND GROUP INFUSED WITH HISTAMINE BASE (1·0 MG)

Control				Histamine-treated			
No.	Sex	Weight (kg)	Period of survival post-endotoxin (h)	No.	Sex	Weight (kg)	Period of survival post-endotoxin
1	F	9·0	16	11	M	13·0	6 h
2	F	10·9	6·5	12	F	10·4	Permanent
3	M	9·2	2·5	13	M	10·3	Permanent
4	M	8·1	2·5	14	M	9·0	Permanent
5	M	9·8	16	15	F	8·7	Permanent
6	M	9·0	16	16	F	8·2	Permanent
7	M	12·3	3·75	17	F	11·6	Permanent
8	F	12·0	16	18	F	15·0	Permanent
9	M	9·7	6·25	19	F	10·0	16 h
10	M	12·5	4·5	20	M	11·0	Permanent

The nature of irreversible endotoxin shock is little understood. The role of histamine and other vasoactive agents, such as the catecholamines, are under further investigation in our laboratory.

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[1] Weil, M. H., and Spink, W. W., *Amer. Med. Assoc. Arch. Int. Med.*, **101**, 184 (1958).
[2] Spink, W., and Potter, R., *Fed. Proc.*, **22**, 628 (1963).
[3] Gilbert, V. E., and Braude, A. I., *J. Exp. Med.*, **116**, 477 (1962).
[4] Hinshaw, L. B., Jordan, M. M., and Vick, J. A., *Amer. J. Physiol.*, **200**, 987 (1961).
[5] Hinshaw, L. B., Emerson, jun., T. E., Iampietro, P. F., and Brake, C. M., *Amer. J. Physiol.*, **203**, 600 (1962).
[6] Spink, W. W., and Vick, J., *Circulation Res.*, **9**, 184 (1961).
[7] Spink, W. W., and Vick, J. A., *Proc. Soc. Exp. Biol. and Med.*, **106**, 242 (1961).
[8] Noah, J. W. and Brand, A., *J. Allergy*, **32**, 236 (1961).
[9] Fox, jun., C. L., and Lasker, S. E., *Amer. J. Physiol.*, **202**, 111 (1962).

Response of Mice to a Chromic Phosphate Injection

FOLLOWING single injections of organic and inorganic particulate material into experimental animals, systemic shock symptoms and numerical shifts in blood cells have been observed. For example, peripheral eosinophilia has been observed in guinea pigs following a single intravenous injection of keratin[1], peritoneal eosinophilia in normal mice following a single peritoneal injection of asbestos fibres[2], and peritoneal eosinophilia in both normal and adrenalectomized mice following a single peritoneal injection of pollen, albumin, horse serum, ascaris extract and keratin[3,4]. The 'macro-molecular syndrome' produced by organic molecules such as proteins, lipids, carbohydrates and combinations of these substances has