of the i.p. injection of uric acid in glutathione-depleted rabbits[13]. The particularly pronounced activity of **2** may also indicate that the actual diabetogenic agent in alloxan-induced diabetes could be formed through a combination of exogenous alloxan with blood urea. The formation of ureide **2** is a characteristic chemical property of alloxan[10] and may become useful in understanding its mode of action.

1 Institute for Diabetes, Endocrinology, and Metabolic Diseases 'Vuk Vrhovac', Medical Faculty, University of Zagreb, Krijesnice b.b., 41000 Zagreb.

2 A. Lazarow, Physiol. Rev. *29,* 48 (1949).
3 R.S. Typson and J.A. Rubens, Archs. Biochem. *8,* 1 (1945).
4 D. Seligson, Fedn Proc. *10,* 124 (1951).
5 M. Ascoli and G.Z. Izar, Hoppe Seylers Z. physiol. Chem. *58,* 529 (1908); Hoppe Seylers Z. physiol. Chem. *62,* 347 (1909).
6 G. Soberon and P.P. Cohen, Archs. Biochem. Biophys. *103,* 331 (1963); and references cited therein.
.7 M. Poje, E.F. Paulus and B. Ročić, J. org. Chem., in press (1979).
8 B. Ročić and M. Poje, J. heterocyclic Chem., submitted.
9 H. Biltz and M. Heyn, Justus Liebigs Annln Chem. *413,* 7 (1916).
10 R. Behrend and R. Zieger, Justus Liebigs Annln Chem. *410,* 337 (1915).
11 H. Biltz and M. Heyn, Chem. Ber. *45,* 1677 (1912); *47,* 459 (1914).
12 G. Brückmann and E. Wertheimer, J. biol. Chem. *168,* 241 (1947).
13 M. Griffiths, J. biol. Chem. *184,* 289 (1950).

Effects of aluminium hydroxide on restraint-induced and restraint delay-induced gastric ulceration in rats

G.B. Glavin

Department of Psychology, Brock University, St. Catharines (Ontario, Canada L2S 3A1), 5 April 1979

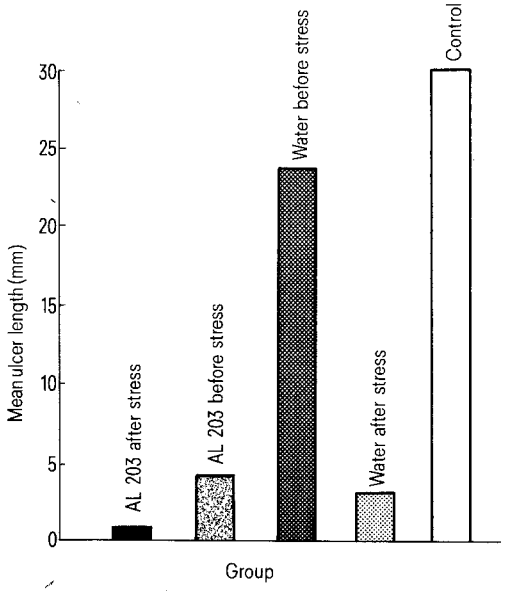
Summary. Rats given aluminium hydroxide after cold-restraint stress but before the 'post-stress delay' period, ulcerated significantly less severely and less frequently than rats given the drug before cold-restraint stress or those given water at either time period. Both aluminium hydroxide treated groups exhibited less ulceration than non-drug groups. These data suggest profound parasympathetic and hence, gastric acid, involvement in restraint delay-induced ulceration in rats.

The use of restraint as an ulcerogenic technique has been extensively documented[1-3]. Recently, a variation of the standard restraint procedure involving a 90-min post-stress delay in sacrificing the animals has been reported to enhance ulceration relative to animals sacrificed immediately following stress termination[4]. A similar phenomenon had previously been reported using shock stress[5,6]. The reasons for this phenomenon are unclear, however, parasympathetic 'rebound' following chronic sympathetic arousal during the stress of restraint is suggested by the work of Mason et al.[7] who observed marked elevation of parasympathetic function in monkeys given rest periods from a prolonged shock avoidance regimen. The present investigation was an attempt to examine the antiulcerogenic effects of a locally-acting antacid (aluminium hydroxide gel Amphojel) administered at various stages of the restraint delay paradigm.

Method. 50 male Wistar rats (175–200 g at the start of the experiment) were used. All animals were starved for 24 h and divided into equally-sized groups.

1 group of rats was given a single oral injection of 300 mg (in 5 ml) of aluminium hydroxide gel (Amphojel) prior to being subjected to the cold-restraint procedure in the supine position[8] for 3 h. Following this period, the animals were removed from the cold-restraint treatment and returned to their home cages without food or water for 90 min. Following this 'post stress delay' period[4-6], the rats were sacrificed with chloroform, their stomachs excised and examined for ulceration. The number, location (rumenal or glandular) and the cumulative length (mm) of the ulcers were recorded. A 2nd group of rats received treatment identical to that of the 1st group, except that the aluminium hydroxide injection was administered after the 3 h period of cold restraint and immediately prior to the 'post-stress delay' period. Rats in a 3rd and 4th group, received the same treatment as those in groups 1 and 2, except that they received oral injections of distilled water prior to or immediately following the 3 h period of supine cold-restraint, respectively. A final group of rats received no injection, but was subjected to both the supine cold-restraint period and the 'post-stress delay' period.

Results. Figure 1 shows mean cumulative glandular ulcer length (mm) for the 5 groups of rats. Rats given aluminium hydroxide prior to the cold-restraint period exhibited significantly less frequent ($p < 0.001$) and significantly less severe ($p < 0.001$) glandular stomach ulceration than either of the water-injected or non-injected groups. Rats given aluminium hydroxide after cold-restraint but prior to the 'post-stress delay' period, displayed significantly less frequent ($p < 0.001$) and significantly less severe ($p < 0.001$) glandular ulceration than any of the other groups. In the case of both aluminium hydroxide and water, administration after cold-restraint stress was more effective in



decreasing gastric damage than was their administration prior to cold-restraint stress.

Discussion. It is clear that antacid drug administration either prior to or immediately following cold-restraint stress reduces ulceration relative to water-treated or non-treated animals. More striking, however, was the finding that antacid administration following stress but prior to 'post-stress delay' had the most significant ulcer-reducing effect. A similar but smaller effect was noticed with water-injected rats. It appears that substances which have a buffering effect in the stomach will exert an antiulcerogenic effect if administered at a time just prior to the 'post-stress delay' period. These results suggest that parasympathetic rebound, and hence, accompanying vagal-stimulated increases in gastric acid secretion, is indeed responsible for the phenomenon of 'post-stress delay' - induced increases in ulcer severity, relative to animals examined immediately following a stress treatment[4–6].

1 R. Ader, Adv. psychosom. Med. *6*, 1 (1971).
2 D. Brodie, in: Peptic Ulcer, p. 71. Ed. C. Pfeiffer. J.B. Lippincott, Philadelphia 1971.
3 G. Glavin and A. Mikhail, Physiol. Behav. *17*, 777 (1976).
4 D. Wozniak, unpublished results, 1976.
5 E. Wald, J. MacKinnon and O. Desiderato, Physiol. Behav. *10*, 825 (1973).
6 O. Desiderato, J. MacKinnon and H. Hissom, J. comp. Physiol. Psychol. *87*, 208 (1974).
7 J. Mason, J. Brady, E. Polish, J. Bauer, J. Robinson, R. Rose and E. Taylor, Science *133*, 1596 (1961).
8 G. Vincent, G. Glavin, J. Rutkowski and W. Paré, Gastroent. Clin. Biol. *1*, 539 (1977).

Evidence against a reflex vasodilation in hemorrhagic hypotension[1]

R.F. Bond, Lorraine C. Peissner and Eva S. Manning[2]

Kirksville College of Osteopathic Medicine, Kirksville (Missouri 63501, USA), 23 March 1979

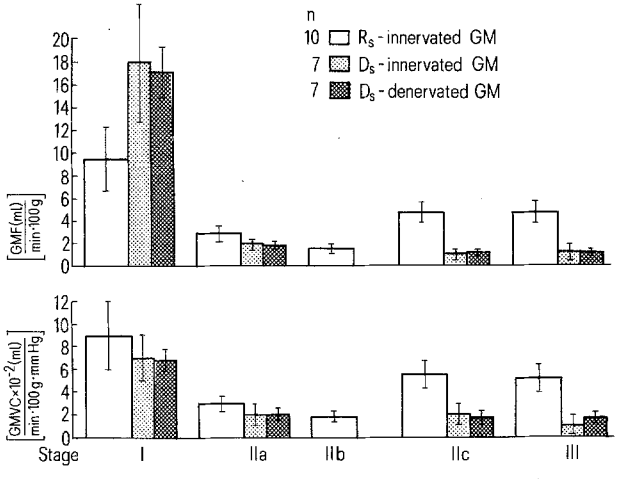
Summary. These studies indicate that the loss of skeletal muscle vascular tone following severe blood loss is not the result of a local reflex initiated by tissue ischemia.

It has long been recognized that severe blood loss results in hypotension and tissue hypoperfusion, and if not corrected early will result in irreversible cellular damage and cardiovascular failure[3]. Studies by our group suggest that a major part of the total cardiovascular decompensation occurs as a result of a paradoxical loss of vascular tone in the skeletal muscle[4–6]. The significance of the peripheral vascular failure has been examined by Rothe and Selkurt[7] who reported a 40% fall in total peripheral vascular resistance between early and late hemorrhagic hypotension. These studies together with recent observations in which we have shown a relationship between vascular decompensation and survival[8] provide evidence that the skeletal muscle vasculature plays a major role in the peripheral vascular failure occurring during severe blood loss. The aim of the present series of investigations was to determine whether or not a local reflex triggered by tissue ischemia may be responsible for the previously reported skeletal muscle vascular decompensation.

Methods and results. To accomplish the stated objectives 3 groups of experiments were conducted using the vascularly isolated cross-perfused canine gracilis muscle preparation reported by us previously[6]. Skeletal muscle blood flow was monitored using an electromagnetic blood flow probe in the venous line draining the vascularly isolated gracilis muscle. Pressures were recorded with the aid of Statham pressure transducers.

The protocol consisted of a controlled step-wise hemorrhage until the shocked animal's mean arterial pressure (MAP) had fallen to 35–40 mm Hg, after which the pressure was maintained by appropriate blood volume adjustments. To facilitate data reduction the basic protocol was divided into the following series of stages. Stage I was the prehemorrhage control; stage IIa was the point during the hemorrhage procedure when the MAP had first reached 35–40 mm Hg; stage IIb was the point during blood loss where maximum skeletal muscle vasoconstriction occurred (or minimum conductance determined by dividing blood flow by perfusion pressure); stage IIc was the point of maximum blood loss during the shock procedure; and stage III was the point when a reinfusion of 25% of the maximum shed blood volume was necessary to maintain MAP at 35–40 mm Hg.

In the 1st group of experiments the recipient animals were subjected to the shock procedure while the vascularly



This histogram represents the hemodynamic response of the vascularly isolated cross-perfused gracilis muscle bed to hemorrhagic hypotension. The 10 R_s-innervated data were taken from experiments in which the gracilis muscle of the shocked recipient animal was perfused by normal donor blood. The D_s data were taken from experiments in which the donor animals were shocked with the result that the arterial blood perfusing the isolated gracilis muscle contained shock elements. This D_s group was further subdivided into innervated and denervated groups. Only the R_s group showed vascular decompensation (vasodilation) in stages IIc and III even though both the innervated and denervated D_s groups had severely compromised flow. The conclusion was reached that vascular decompensation was not the result of a local reflex initiated by tissue ischemia. GMF is gracilis muscle blood flow and GMVC is gracilis muscle vascular conductance. The data is presented as mean ± 1 SEM.