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Direct activation of platelets by heat is the possible trigger of the coagulopathy of heat stroke

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Summary. The trigger of the coagulopathy that complicates heat stroke is obscure, but direct platelet activation by heat is a possibility we set out to study. Platelet rich plasma (PRP), prepared from blood donors, was incubated at increasing temperatures (38–45°C) and then platelet aggregation was undertaken in response to decreasing low doses of ADP (<2·0 μmol/l). Hyperaggregability was manifested when the incubation temperature reached 43°C and was maximum at 44°C before complete inhibition of responses at 45°C.

The platelet hyperactivity induced by heating at 44°C persisted after reincubating PRP samples at 37°C. These platelet responses could not be triggered in PRP samples prepared from subjects after the overnight ingestion of aspirin or after the addition of aspirin to PRP before starting the heating procedure. However, aspirin was less effective when added to PRP after the appearance of the heat-induced hyperaggregability.

In conclusion, these results indicate that platelets can be activated directly by heat. This mechanism which may be operational in heat stroke, is unaffected by cooling (body cooling being basic in the management of heat stroke) but can be prevented by the early administration of aspirin.

In recent years heat stroke has become a leading cause of morbidity and mortality among pilgrims to Makkah, especially when the annual pilgrimage (Haj) occurs during the hottest months of the year (May–August) when maximum mid-day temperature can be as high as 48°C (Khogali & Al Khawashki, 1981; Al-Aska *et al.* 1987). Haemorrhagic complications in heat stroke patients are common clinical findings, variable in severity from simple increased tendency, e.g. prolonged bleeding from venepuncture sites, to more severe bleeding from multiple sites often with fatal outcome (Khogali, 1983). The pathogenesis of this haemostatic failure has been ascribed to disseminated intravascular coagulation (DIC) (Weber & Doan, 1939; Stefanini & Spicer, 1971; Perchik *et al.* 1975; Chao *et al.* 1981; El-Kassimi *et al.* 1986; Musatafa *et al.* 1983, 1985), primary fibrinolysis (Stefanini & Spicer, 1971; Mustafa *et al.* 1983, 1985; Meikle & Graybill, 1967) as well as failure of synthesis of coagulation factors by the liver (Wright *et al.* 1946).

The trigger to these haemostatic abnormalities in heat stroke is still not clearly defined. Recent evidence accumulated from coagulation studies in cancer patients exposed to therapeutic hyperthermia indicates that platelet activation and thrombin generation are early events (Strother *et al.* 1986). This raises the question whether heat directly activates platelets leading to secondary recruitment of fluid phase coagulation.

Previous *in vitro* studies on the effect of heat on platelet behaviour were scanty and inconclusive (Ogston & Taylor, 1980; White, 1968). However, in preliminary studies in heat stroke patients, we recorded platelet aggregation responses ranging from hyperaggregability to inhibition of responses. This raised the possibility that marked alteration of platelet function may be associated with heat stroke. In the following account we describe these preliminary findings as well as the results of an *in vitro* approach studying platelet aggregation responses in platelet rich plasma (PRP) incubated at increasing temperatures ranging from 37°C to 45°C. We were able to demonstrate that heat can directly activate platelets, and provoke hyperaggregability, followed by complete inhibition of platelet aggregation responses. The heat-induced hyperaggregability persisted after reincubating PRP at 37°C, but could not be provoked in the presence of the antiplatelet drug, aspirin.

MATERIALS AND METHODS

(a) *Platelet aggregation in heat stroke patients.* Platelet aggregation in heat stroke patients was undertaken as part of the haematological investigations carried out during Haj, in 34 heat stroke patients on their admission to the Heat Stroke

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Table 1. Physical characteristics of patients with heat stroke (n = 34)

Age ($\bar{x}$ ± SD): 58·1 ± 8·1 years; range 40–75 years
Rectal temperature ($\bar{x}$ ± SD): 41·9 ± 0·8°C, range 40·1–43·3°C
Sex: males = 18; females = 16
Nationalities

Egyptians	= 9	Asians	= 7	North African Arabs	= 6
West Africans	= 5	Turks	= 3	Saudis	= 2
Other Arabs	= 2				

Centres in Mina and Arafat, Makkah, Saudi Arabia. The physical characteristics of these patients are shown in Table 1. Blood samples for haemostatic studies were collected with the minimum of venous stasis and transferred to plastic tubes containing sodium citrate (3·8%, 0·11 M), to give a blood : citrate ratio of 9 : 1. Platelet rich plasma was separated at room temperature by centrifugation at 125 g for 10 min and platelet aggregation was performed within 2 h of blood collection.

(b) *Effect of heat on platelet aggregation.* This initial part of the *in vitro* studies was designed to find out whether platelets can be activated directly by heat, and if so, the critical temperature at which heated platelets display hyperaggregability. Blood was collected from five healthy volunteers and added to citrate anticoagulant. PRP was separated, and divided into two parts: one part was incubated in a water bath at 37°C to serve as a control, while the second part was placed in another water bath which was heated to a selected incubation temperature. Temperatures studied were 38, 39, 40, 41, 42, 43, 44 and 45°C. Subjects were tested twice every week and the test was carried out at a different incubation temperature each time, with a 37°C control running simultaneously, until tests were completed for the whole range of temperatures. Platelet aggregation was performed at 30, 60, 90, 120 and 150 min after the start of incubation.

(c) *Effect of cooling heated hyperaggregable platelets.* PRP samples obtained from six volunteers were incubated at 44°C with a 37°C control running simultaneously, and ADP dose–response aggregometry was undertaken at 7·5 min intervals. Once hyperaggregability was manifested, usually after 30 min incubation at 44°C, PRP was reincubated in a water bath at 37°C and aggregation was carried out at 15, 30, 60, 90 and 120 min thereafter.

(d) *Effect of antiplatelet drugs in vivo.* Five subjects who had participated in most of the previous experiments and were well acquainted with the objectives of the study, were given 100 mg aspirin (Bayer) the night before blood sampling. Next morning, blood was collected and the experimental protocol was repeated, i.e. heating at 44°C for 30 min followed by cooling at 37°C.

(e) *Effect of antiplatelet drugs in vitro.* (i) Aspirin at a final concentration of 50 μg/ml was added to PRP before performing the standard experimented protocol described above. Complete inhibition of arachidonic acid induced platelet aggregation was taken as the indicator of the efficacy of aspirin action.

(ii) Five PRP samples which displayed hyperaggregability to ADP, 30 min incubation at 44°C and then cooling at 37°C were subsampled and aspirin at a final concentration 50 μg/ml was added to the PRP in an aggregation tube. The tube was allowed to stand at 37°C for 2 min before ADP dose–response aggregation was undertaken. Total inhibition of arachidonic acid aggregation was also taken as a guide to complete blocking of the prostaglandin pathway of platelet activation.

Platelet aggregometry. Platelet aggregation was carried out in response to decreasing doses of ADP (20, 2·0, 1·0, 0·5, 0·25 μM/l), arachidonic acid (1·64 mmol/l) and adrenaline (100 μM/l). All concentrations represent final concentrations obtained by adding 20 μl of the aggregating agent to 180 μl PRP. Aggregation was determined by the usual turbometric method and was recorded in the four channel Aggregation Profiler PAP4 (Bio/Data, U.S.A.) which automatically measures and registers maximum aggregation percentage as well as the slope of the aggregation curves. This procedure was detailed recently (Gader *et al.* 1988).

Statistical methods. The Student's *t*-test was employed for establishing the significance of the observed differences. A P value of 0·05 or less was considered statistically significant.

RESULTS

The index of platelet hyperactivity in this study is the presence of hyperaggregability, i.e. irreversible platelet aggregation responses to decreasing ADP doses which are too low to affect resting non-stimulated platelets (Pitney, 1981).

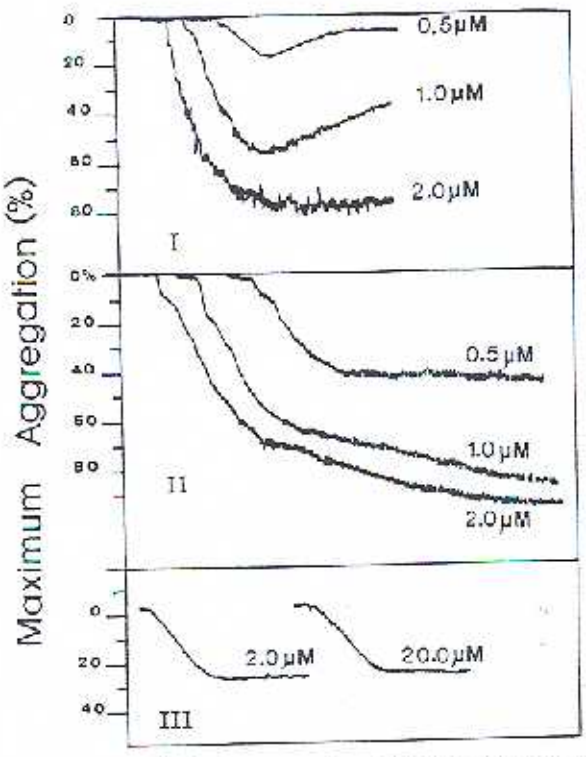

Fig 1. Records of the platelet aggregation responses to ADP (20, 2·0, 1·0 and 0·5 μM), in three heat stroke patients. (I) Normal ADP aggregation; (II) hyperaggregation; (III) abnormal (inhibited) response.

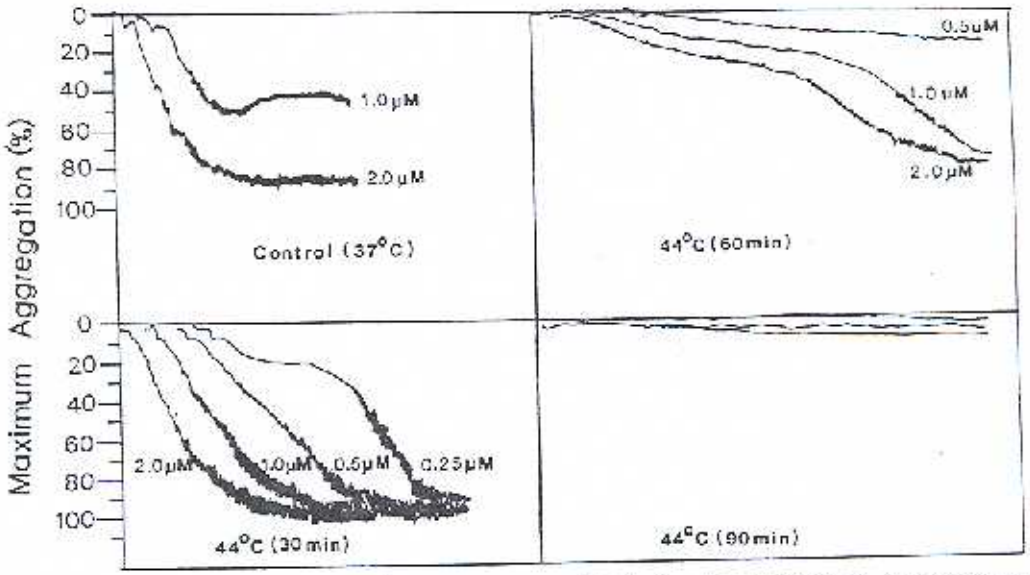

Fig 2. The effect of heat on platelet aggregation *in vitro*. Responses were recorded after incubating PRP for 30, 60 and 90 min at 44°C in the presence of ADP (2·0, 1·0, 0·5, 0·25 μM). A 37°C control is included.

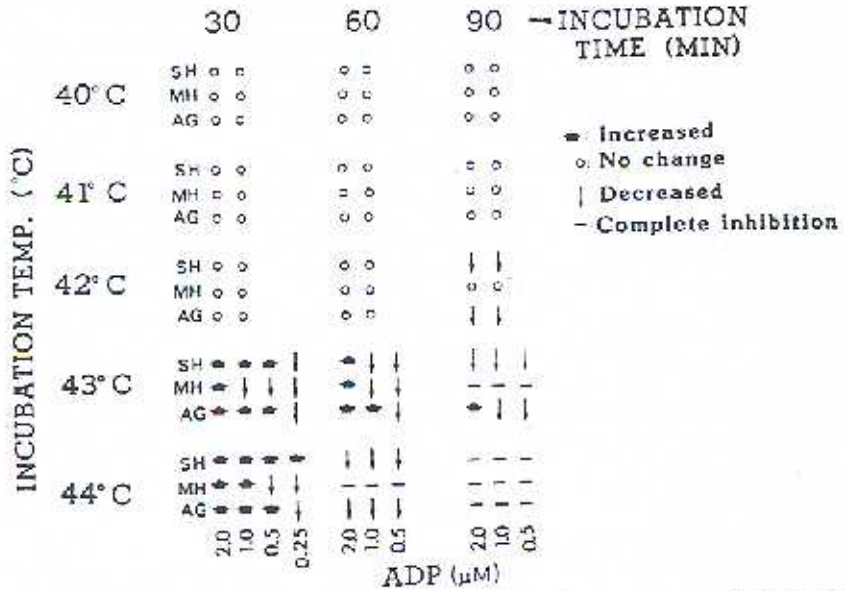

Fig. 3. Diagramatic representation of the effect of temperature on ADP aggregation in three volunteers. SH, MH and AG. Results represent the difference between the maximum aggregation (%) at 44°C and 37°C.

The aggregation tracings shown in Figs 1, 2 and 5 are representative of the changes recorded in individual experiments.

(a) *Platelet aggregation in heat stroke patients*

A wide spectrum of aggregation responses to ADP were obtained (Fig 1) ranging from hyperaggregability ($n=12$) normal responses ($n=6$) and inhibited responses ($n=16$). 26 of these patients had no bleeding manifestation at presentation while the rest ($n=8$) presented with bleeding symptoms ranging from mild ecchymoses, prolonged bleeding from venepuncture sites, epistaxis and purpuric rash to more severe bleeding from multiple sites, gum bleeding, haematuria haemoptysis and haematemesis. There was, however, no direct relationship between the occurrence of bleeding manifestations and the nature of the platelet aggregation responses, platelet count, body temperature or nationality. The precooling platelet counts in these patients ranged from 113 to 436×10^9/l ($\bar{X}\pm SD=251\pm97{\cdot}1$) and therefore thrombocytopenia was discarded as a cause of the abnormal bleeding.

(b) *Effect of heat on platelet aggregation* (Figs 2 and 3)

When PRP samples were incubated at 37, 38, 39, 40, 41 and 42°C, platelet aggregation responses were unchanged in the

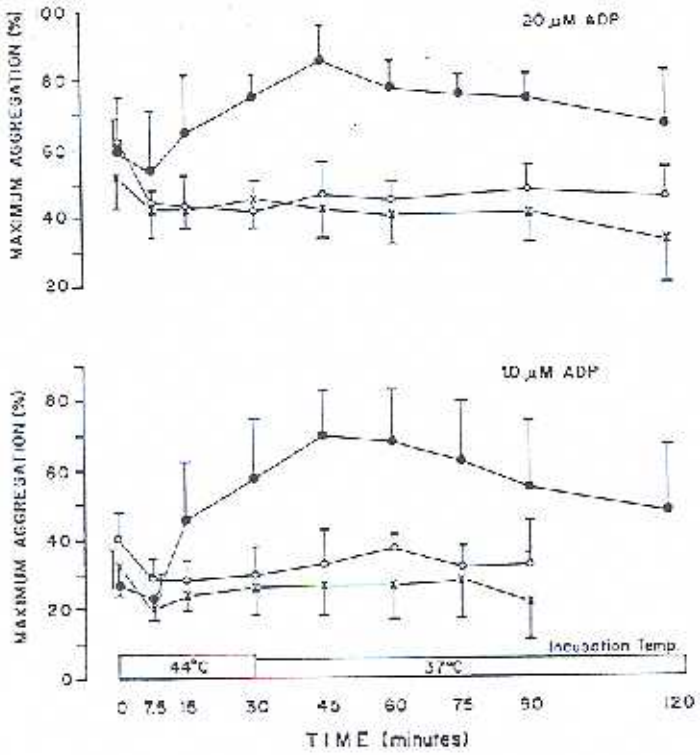

Fig 4. Results of platelet aggregation responses to ADP (2·0 and 1·0 μM) expressed as mean ± SD of maximum aggregation (%), showing the effect of heating PRP at 44°C for 30 min and then reincubating at 37°C. ●, without aspirin; ○, after the overnight ingestion of aspirin (aspirin *in vivo*); ×, aspirin added to PRP before starting the heating procedure (aspirin *in vitro*).

Table II. The effect of aspirin *in vitro* on heat-induced platelet aggregation in response to ADP 2·0 and 1·0 μM. Results are expressed as mean ± standard deviation of maximum aggregation (%)

		Incubation time (min) at 44°C			Reincubation time (min) at 37°C			
	Resting	15	30	15	No aspirin 30	Aspirin 30	No aspirin 45	Aspirin 45
ADP 2·0 μM	69·8 ±23·4	65·8 ±15·9	80·0 ±5·7	77·8 ±5·3	80·6 ±6·9	51·4* ±13·1	73·4 ±5·7	50·6* ±7·4
ADP 1·0 μM	48·6 ±22·1	55·0 ±25·1	65·2 ±25·7	63·4 ±26·3	63·6 ±21·4	36·6* ±11·3	49·4 ±23·7	36·2** ±9·4*

* $P<0·01$; ** $P<0·05$.

first hour of incubation but some samples showed slight inhibition afterwards. Hyperaggregability started to show in most samples after 30 min incubation at 43°C and was more pronounced at 44°C; thereafter platelet responses were markedly inhibited. No responses could be evoked at 45°C.

(c) *Effect of cooling* (Fig 4)

There was significant enhancement of the platelet aggregation responses to ADP (2·0 and 1·0 μM) when PRP samples were incubated at 44°C for 30 min ($P<0·05$), as compared to the responses obtained before exposing platelets to heat. These responses were enhanced further ($P<0·001$) when PRP was reincubated at 37°C for 15 min. Thereafter, the responses showed a gradual diminution but remained above the resting level ($P<0·05$) for up to 90 min reincubation at 37°C.

(d) *Effect of antiplatelet drugs in vivo*

There was complete inhibition of the platelet release reaction as shown by the lack of the platelet aggregation responses of arachidonic acid and the presence of only primary phase aggregation in response to high dose ADP and adrenaline. In all subjects, heating platelets at 44°C has failed to induce any degree of platelet activation (Fig 4).

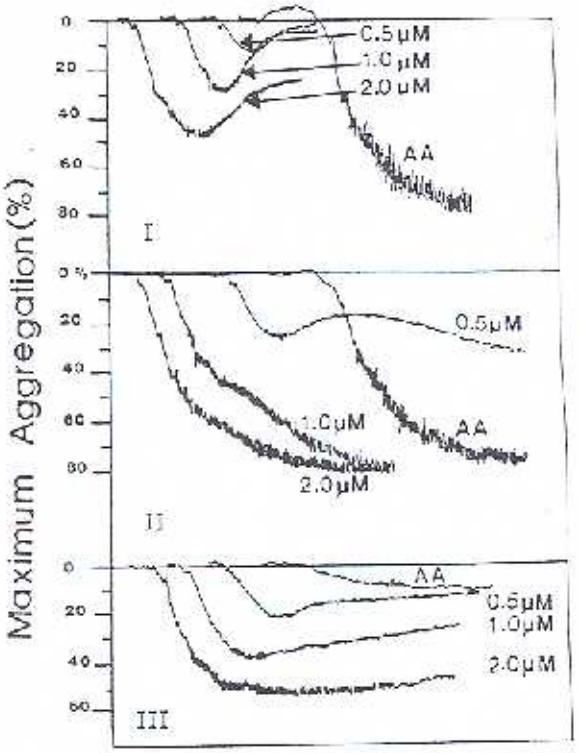

Fig 5. The effect of aspirin *in vitro* on the platelet aggregation responses to decreasing doses of ADP: 2, 1 and 0·5 µM and arachidonic acid (AA). (I) Control: before heating PRP. (II) PRP heated for 30 min at 44°C and then reincubated at 37°C, showing hyperaggregability. (III) Same as (II) but aspirin was added 2 min before ADP or AA.

(e) *Effect of antiplatelet drugs in vitro*

The addition of aspirin to PRP before starting the aggregation procedure caused complete blocking of the heat-induced enhancement of the aggregation responses to ADP (Fig 4). However, when aspirin was added to activated, hyperaggregable platelets, and despite complete inhibition of the arachidonic acid responses, platelets continued to display irreversible aggregation to decreasing doses of ADP (Fig. 5). The results obtained are summarized in Table II.

DISCUSSION

Perturbations of various components of the haemostatic system in victims of heat stroke are widely reported (Weber & Doan, 1939; Stefanini & Spicer, 1971; Perchik *et al*, 1975; Chao *et al*, 1981; El-Kassimi *et al*, 1986; Mustafa *et al*, 1983, 1985; Meikle & Grayhill, 1967; Shibolet *et al*, 1982; Wright *et al*, 1946) but none of these studies included platelet function. In this study the results obtained in heat stroke patients on their arrival at hospital showed platelet aggregation responses ranging from hyperaggregability, unchanged or normal, to inhibited responses. This wide variation in the aggregation responses may be a reflection of the various stages of the *in vivo* platelet activation process in individual patients. This raises the possibility that heat acting on quiescent platelets triggers the activation process, as indicated by the enhanced responses to decreasing doses of ADP (hyperaggregability) (Pitney, 1981); then platelets undergo the secretion stage and finally loose their responsiveness to ADP and other aggregating agents. This may be the underlying explanation for the wide variation in the aggregation responses obtained in individual patients.

Our *in vitro* experiments give support to this suggestion. When platelets were heated *in vitro* the phenomenon of hyperaggregability was obtained only when the incubation temperature reached 43°C. At this temperature, platelets from all subjects started to show irreversible aggregation in response to decreasing ADP doses which had no such effect on platelets incubated at lower temperature. More pronounced platelet responses were obtained at 44°C. However, after 30 min incubation at 43°C and 44°C, platelets no longer responded to ADP. Incubation at 45°C for any length of time caused complete inhibition of platelet aggregation.

White (1968) studied the effect of heat on platelet function and employed direct visualization for detecting aggregation which was manifested as 'a snow storm of platelet particles'. He found that platelets exposed to temperatures upto and including 42°C for 15 min appeared to aggregate normally in response to ADP. However, aggregation was reduced at 43°C and completely inhibited at 44°C and 45°C. Using the more precise and objective turbometric aggregometer, our results confirm the findings of White, that no change in platelet aggregation occurs when platelets are incubated at temperatures up to 42°C. However, White did not detect the enhanced aggregation responses we were able to record at 43°C and 44°C. This initial hyperaggregability was followed by complete inhibition of responses.

White has also investigated the effect of heat on platelet morphology (White, 1968). He found no evident morphologic alterations in platelets exposed to temperatures upto 42°C. However, at higher temperatures of 43–45°C the morphologic transformations observed included the loss of the discoid shape, and shifting of the storage organelles from their random location to the cell centres, where they become enclosed within a ring of microfilaments and microtubules. These transformations which could not be reversed by cooling platelets to 37°C (White, 1968), have been confirmed in platelets which have undergone irreversible aggregation induced by a variety of aggregating agents (White, 1984).

It is evident, therefore, that when platelets are exposed to the stress of heat they become more responsive to stimulation by decreasing doses of ADP only at 43°C and 44°C and the hyperactivity cannot be reversed by cooling to 37°C. In the same temperature range they also show morphological changes known to accompany agonist-induced platelet activation and irreversible aggregation.

Whether the progressive *in vitro* effects of heat on platelet aggregation, described above, will develop in the same way *in vivo*, in heat stroke patients, is open to speculation. However, whole body hyperthermia (WBH) which is used as an antineoplastic treatment in cancer patients (Strother *et al*, 1986) introduces changes in the coagulation system that could be extrapolated, with caution, to the heat stroke situation. These patients are heated up to a core temperature of 41·8°C, and maintained at this temperature for 2 h before

they are allowed to cool. Significant elevation of the plasma levels of the platelet proteins βTG and PF4 were noted 2 h after starting the heating procedure and just before cooling the patients. Measurements of the plasma coagulation parameters performed simultaneously were indicative of a consumption coagulopathy. In WBH, therefore, platelet activation is an early event and this prompted the authors to raise the question whether heat can directly activate platelets leading to secondary recruitment of fluid phase coagulation (Strother *et al.* 1986).

The results of our *in vitro* studies, which followed a different way of monitoring platelet function, viz platelet aggregation, confirm that heat can directly enhance platelet function. If the heating process continues platelets eventually lose their ability to respond to aggregating agents and become totally inhibited. Such a mechanism may be operational in heat stroke patients, and therefore may explain the aggregation responses recorded in our heat stroke patients.

The stress of exposure to heat is accompanied by an increase in the levels of catecholamines, adrenaline and noradrenaline (Robertshow & Whittow, 1966), which enhance platelet responses to aggregating agents *in vitro* and *in vivo* (Jones *et al.* 1985). In addition the metabolic derangements accompanying heat stroke, e.g. acidosis, hypoxaemia, dehydration and others (Khogali, 1983) are the same factors known to lower the threshold for the development of DIC (Cash, 1977). When these stress factors are compounded by the direct effect of heat on platelets, it may not be necessary for body temperature to increase to as much as 43–44°C for heat to provoke platelet activation and/or DIC. The patients whom we studied had rectal temperatures ranging from 41°C to 43·3°C, but temperatures as high as 44°C have been recorded in heat stroke patients (Khogali & Al Khawashki, 1981).

The effect of the antiplatelet drug, aspirin, on these platelet responses raises many points of interest on the mechanism of activation of platelets by heat and the possibility of its therapeutic use in heat stroke. When aspirin was given before exposing platelets to heat, whether *in vitro*, by adding it to PRP, or *in vivo*, by asking volunteers to ingest it 12–15 h before sampling, heat no longer induced hyperaggregability. This indicates that the prostaglandin pathway may be involved, either in the initial stages of platelet activation by heat or in the development of the heightened responses that follow thereafter. On this basis, aspirin may be useful in preventing the coagulopathy of heat stroke by inhibiting platelet activity in the same manner that has been suggested recently by its preventive action on the DIC induced by *S. aureus* in animals (Nussbaum *et al.* 1988).

Aspirin in a dose that blocks the prostaglandin pathway of platelet activation, as evidenced by complete inhibition of arachidonic acid aggregation responses, causes partial blocking of the already established heat-induced responses of platelets to decreasing doses of ADP. These results suggest that the heat-induced platelet activity is mediated by at least two different mechanisms, only one of which is sensitive to aspirin and this could be the prostaglandin pathway of platelet activation. The second may be a mechanism of intrinsic membrane modulation (Rao *et al.* 1980) for securing irreversible aggregation in the presence of aspirin, i.e. it is independent of prostaglandin synthesis. This mechanism was proposed by Rao *et al* to be responsible for triggering irreversible aggregation of aspirin-treated human platelets, when exposed initially to too low doses of epinephrine, which restores their sensitivity to ADP.

The results obtained in this study lead us to the following conclusions: (1) heat can activate platelets directly; (2) once activated, platelets will not regain the resting state by cooling; (3) antiplatelet therapy (aspirin) may be helpful in preventing the development of coagulopathy of heat stroke. This last observation suggests that the early commencement of anti-platelet (aspirin) therapy should be considered in the management of heat stroke, along with other established measures such as body cooling and rehydration (Al Aska *et al.* 1987), and well before bleeding manifestations become the overwhelming clinical presentation.

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