Platelet function, factor VIII, fibrinogen, and fibrinolysis in Nigerians and Europeans in relation to atheroma and thrombosis

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SUMMARY Platelet function, factor VIII, fibrinogen levels, and fibrinolysis were studied in Europeans and in two groups of Nigerians living in Zaria, northern Nigeria, in order to see whether differences could help to explain the low incidence of atheroma and thrombosis in Nigerians. We confirmed the relative thrombocytopenia and observed a rapid disaggregation after ADP-induced platelet aggregation in Nigerians. The most striking difference was a reduced or absent ristocetin-induced platelet aggregation in Nigerian platelet-rich plasma, probably due to a plasma component interacting with the von Willebrand activity (VWF), since factor VIII coagulant activity, factor VIII related antigen, and isolated VWF were normal or high by European standards. Group II (rural population), but not group I (senior university staff in Zaria) of the Nigerians, tended to have high serum fibrinogen concentrations. Spontaneous fibrinolytic activity was enhanced in most Nigerians compared to the Europeans and was normally increased after venostasis in proportion to the initial activity. Fibrinolysis and ristocetin-induced platelet aggregation values for the Nigerians in group I were intermediate between European and Nigerian in the group II values, suggesting that differences were due more to environmental than to genetic factors.

Relative thrombocytopenia, disaggregation after ADP-induced aggregation, inhibition of ristocetin-induced platelet aggregation, and active fibrinolysis help to explain the infrequency of thrombotic disease in Africans. Also the low incidence of atheroma may follow from less platelet adherence and less platelet release of mitogenic factors, which cause intimal hyperplasia.

There are wide geographical and racial differences in the incidence of atheroma (Restrepo, 1974; Shaper, 1974). It is rare in Nigerians (Parry and Ikeme, 1966; Edington and Gilles, 1975), and Akinkugbe (1972) reported 240 hypertensive patients in Ibadan (southern Nigeria) without any coronary accident during a two-year period of study; no ischaemic heart lesions were found at necropsy in 29 of these subjects.

As a population living on the Andes plateau presented no arterial thrombosis and their platelets did not respond to aggregating agents (Caen *et al.*, 1971), we decided to compare the haemostatic mechanisms of Nigerians and Europeans living in northern Nigeria.

Subjects

We compared one European group taken as a control with two groups of Nigerians.

EUROPEANS (CONTROLS)

We examined eight Europeans who had lived in Zaria for at least two years and 22 Europeans living in Paris.

NIGERIANS GROUP I

We studied 16 Nigerians, senior staff of the University of Ahmadu Bello (Zaria). They came from the south and north of Nigeria and their ethnic origin was either Ibos or Haoussa. Their life style and customs were similar to those of the Europeans, including their diet and way of life.

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NIGERIANS GROUP II

We examined 30 Nigerians who were blood donors and could be considered representative of the rural population of the Guinea savanna area of northern Nigeria. The ethnic origin of these Nigerians was Haoussa. They were mainly farmers or agricultural workers, their diet was less 'rich' than that of group I, and their serum cholesterol levels were lower. As a consequence of their occupations, the amount of physical exercise of this group was higher than that of the Europeans and group I Nigerians.

Methods

Blood samples (9 vol) were collected by venepuncture into 1 vol sodium citrate 38 g/l. The techniques that were applied have been described by Caen *et al.* (1975).

The platelet count was performed using Unopettes (Becton-Dickinson) and phase-contrast microscopy. Platelet aggregation was studied in a Bryston aggregometer (Labintec, Montpellier, France) on platelet-rich plasma (PRP) and on platelets isolated on an albumin-gradient, according to the method of Nicholls and Hampton (1972), as modified by Levy-Toledano and Bodevin (Caen *et al.*, 1975). Albumin-gradient isolated platelets were resuspended in either their own platelet-poor plasma (PPP) or in a solution of human fibrinogen (Kabi AB, Stockholm, Sweden) 2.5 g/l final concentration and gamma-globulins (Cohn fraction 1, Centre National de Transfusion Sanguine, Paris, France) 4 g/l final concentration as aggregation-cofactors, and aggregation was expressed in terms of velocity and intensity. The aggregation in PRP was induced by the following agents: collagen (Stago, Asnières, France) 8 mg/l final concentration; ADP (Stago) 1.2 μ mol final concentration; ristocetin (Lundbeck, Copenhagen, Denmark) 1 g/l final concentration. With albumin-gradient the same concentration of ristocetin was used, but the final concentration of ADP was 25 μ mol.

Factor VIII coagulant activity (VIII_C) was measured in a one-stage assay using partial thromboplastin time and a haemophilic PPP as a substrate. von Willebrand factor (VWF) was tested by ristocetin-induced platelet-aggregation using the Weiss method slightly modified (Caen *et al.*, 1975). VWF was determined in whole plasma and in plasma-fractions isolated after filtration on Sepharose 2B by which the high molecular weight fraction VWF was eluted in the void volume and separated from many other plasma-proteins. Factor VIII-related antigen (VIII_{RA}) was measured by the Laurell electroimmunodiffusion method using a commercial

anti-human factor VIII antiserum (Behringwerke, Marburg, Germany).

Fibrinogen levels were estimated, and the euglobulin-lysis time was determined before and after venostasis (Lacombe *et al.*, 1971).

Results

PLATELETS

The platelet count was $200 \times 10^9/l$ ($200\,000/\mu l$) or more in all Europeans except one. Five out of 16 Nigerians in group I and 10 out of 30 Nigerians in group II had counts of less than $150 \times 10^9/l$ ($150\,000/\mu l$) (Fig. 1).

Platelet aggregation induced by ADP 1.2 μ mol was followed by spontaneous disaggregation in 12 out of 34 Nigerians of both social groups but was not seen in any of the Europeans. ADP-induced aggregation of isolated platelets from 12 Nigerians in group II was similar to that of 20 Europeans (tested in Paris) when resuspended either in their own plasma or in fibrinogen/gamma-globulin solution (Table 1).

The most striking difference between the Europeans and Nigerians was observed using ristocetin

Fig. 1 Platelet counts in Europeans and Nigerians, groups I and II, in Zaria.

Table 2 Effects of Nigerian group II and European plasma on ristocetin-induced aggregation of control European washed platelets

Ristocetin (1 mg/ml)-induced aggregation with normal washed platelets	Velocity (%)
+ 4 European plasma (half diluted)	70 ± 8
+ 19 Nigerian plasma (half diluted)	40 ± 8

Table 3 Factor VIII activities and ristocetin-induced platelet aggregation in two Nigerians (group II)

	Subject 1		Subject 2	
	Whole plasma	Void volume	Whole plasma	Void volume
VWF activity (U/dl)	0(6)*	70(48)†	0(10)*	80(65)†
Factor VIII _C activity (U/dl)	120		105	
Factor VIII _{RA} (U/dl)	200		200	

*Ristocetin-induced platelet aggregation in presence of whole plasma.

†Ristocetin-induced platelet aggregation in presence of globulins + fibrinogen.

were in normal or high concentration (Table 3). The ristocetin-cofactor activity appeared in whole plasma to be 0 U/dl in both, but their void volume separated by Sepharose 2B filtration contained activity of 70 and 80 U/dl; such results strengthen the hypothesis of the existence of an inhibitor.

FIBRINOGEN

The fibrinogen level was less than 5 g/l in 22 out of 30 Europeans tested and between 5.4 and 6.9 g/l in three living in Zaria. The values in group I Nigerians were in the same range as those of the Europeans (Fig. 4), but 17 out of 30 group II Nigerians had fibrinogen levels above 5 g/l (5.2-8.4 g/l).

FIBRINOLYSIS

The euglobulin-lysis time was 180 minutes or more in the 30 Europeans (Fig. 5). Two out of 13 group I Nigerians had similar results, but six had enhanced spontaneous fibrinolytic activity (lysis time 120 minutes or less). There was an even more striking difference in group II Nigerians, of whom 16 out of 25 had a euglobulin-lysis time of 90 to 120 minutes. The figure of 22 Nigerians with a euglobulin-lysis time of 120 minutes or less was significantly different from the number of Europeans ($P < 0.01$).

The euglobulin-lysis time was repeated after venostasis in nine Nigerians in group II, of whom five had a spontaneous euglobulin-lysis time of 150 minutes or more and four had shorter times. All had a normal enhancement of fibrinolytic activity approximately in proportion to their spontaneous activity (Table 4).

Fig. 4 Fibrinogen levels in Europeans and Nigerians, groups I and II, in Zaria.

Discussion

The present observations (Fig. 1) confirm that the platelet count of symptom-free Nigerians is frequently lower than the internationally accepted normal range of $150-400 \times 10^9/l$ ($150\ 000-400\ 000/\mu l$) (Dacie and Lewis, 1975) in both the forest and derived savanna areas of the south (Essien *et al.*, 1973; Udezo and Odfelt, 1974; Isaacs-Sodeye *et al.*, 1975) and in the Guinea savanna of the north of Nigeria (Atanu *et al.*, 1974). Nigerian newborns have counts which are similar to those of European newborns and higher than those of adult Nigerians (Effiong *et al.*, 1976), which suggests strongly that the relative thrombocytopenia in adults is acquired. The platelet count falls after acute *Plasmodium falciparum* (Beale *et al.*, 1972; Skudowitz *et al.*, 1973; Essien and Oruamabo, 1976) and *P. vivax* parasitaemia (Hill *et al.*, 1964; Beale *et al.*, 1972): various mechanisms are involved, including direct invasion of platelets (Fajardo and Tallent, 1974),

PRP contains an inhibitor of the adhesion of platelets to glass beads. High concentrations of fibrinogen *in vitro* inhibit ristocetin-induced platelet aggregation (Stibbe and Kirby, 1976), but the raised fibrinogen levels in the plasma of group II Nigerians (Fig. 4) probably would not be sufficient to explain the observed lack of aggregation. Macroglobulins such as dextran are also known to inhibit ristocetin-induced platelet aggregation (Åberg *et al.*, 1975). Nigerians have an average high plasma gamma-globulin, including IgM and other macroglobulins, elevations being greater in rural than in urban populations and in group II than in group I (Edozien *et al.*, 1960; Mohammed *et al.*, 1973). It is suggested that ristocetin-induced aggregation could have been inhibited in Nigerians by these plasma-proteins. Alternatively, as the ratio factor VIII_{RA}/VWF was high, there could have been an excessive synthesis by endothelial cells (Jaffe *et al.*, 1973) of a functionally abnormal VIII_{RA} protein or of a normal protein which was inactivated or degraded. Factor VIII degradation products could also interact with normal VWF and inhibit platelet aggregation induced by both ristocetin and ADP (Culasso *et al.*, 1974).

Many studies have shown that the fibrinolytic activity is enhanced in Africans compared to Europeans (Antonis and Bersohn, 1961; Menon, 1967; Szczeklik *et al.*, 1975). Black but not white Americans demonstrated a decrease of resting fibrinolytic activity and alpha-1-antitrypsin with a rise in social class (Franz *et al.*, 1975). Similarly, the spontaneous fibrinolytic activity was greater in group II than in group I (Fig. 5). It was enhanced normally by venostasis in proportion to the initial activity (Table 4), which agrees with the observation of Franz *et al.* (1975) of greater activator-activity in the venous walls of blacks than whites in South Africa. This high spontaneous fibrinolytic activity with a normal response to venostasis could be associated with more frequent and strenuous muscular exercise, diets low in unsaturated fats and with high residue (Barr *et al.*, 1973; Burkitt, 1972), or the particular healthy endothelium in Nigerians with few atheromatous lesions (Akinkugbe, 1972).

The relative freedom of Africans in a rural environment from the complications of atheromatous disease is well established, and the roles of diet and physical activity have been extensively discussed. An immunity from the complications of thrombosis may be explained to a large extent by the low platelet count, early disaggregation after ADP-induced platelet aggregation, inhibition of ristocetin-induced aggregation with a possible *in vivo* modification of the platelet-VWF-subendothelial interaction, and high fibrinolytic activity. In addition, the present observations suggest a

mechanism preventing the formation of atheroma itself. When the endothelium is damaged, platelets adhere to subendothelial tissue and undergo degranulation; this is followed by proliferation of smooth cells, which appears to be the response to a mitogenic agent released by platelets (Ross *et al.*, 1974; Fuster *et al.*, 1975; Busch and Westermark, 1975; Harker *et al.*, 1976). It may be hypothesised that inhibition of the interaction of platelets, VWF, and subendothelium could protect Africans against the development of intimal hyperplasia and atheroma, as the platelets are not strongly adherent and there is only limited release of the mitogenic agent. This mechanism has been postulated to explain immunity from atheroma in pigs with von Willebrand's disease (Bowie *et al.*, 1975).

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