Thrombocytopenia in Malaria with Immunoglobulin (IgM) Changes

P. J. BEALE, J. D. CORMACK, T. B. N. OLDREY

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Summary

Of 33 cases of naturally occurring human malaria 32 were found to have significant thrombocytopenia. Only one patient showed signs of bleeding. The lowest platelet levels were found between the day of diagnosis and the fourth day of treatment. Thereafter they returned to normal values. No other factors could be found to correlate with the presence or depth of thrombocytopenia, and no evidence of intravascular coagulation was found in any case. A rise in the immunoglobulin IgM was found in all 13 cases in which it was estimated. Since thrombocytopenia can occur independently of intravascular coagulation the latter should be diagnosed and heparin given only after clotting factors have been shown to be depleted.

Introduction

During the routine handling of cases of malaria in the British Military Hospital, Singapore, instances of significant thrombocytopenia were observed. Initially the suggestion was entertained that the platelet depression was due to a drug effect, but against this was the rapidity with which the platelets recovered. Further instances of thrombocytopenia occurred in malarious patients who developed epistaxes (three cases) and haematuria (one case). In all of these patients extensive investigation showed no other haematological cause for their bleeding.

A preliminary review of the literature indicated that observations relating to thrombocytopenia in malaria were comparatively recent and that there was a divergence of opinion regarding its pathogenesis.

Dennis *et al.* (1967) examined patients with chloroquine-resistant falciparum malaria, who had relapsed while residing in the United States, and related the thrombocytopenia they observed to defects in various clotting factors. They postulated that the platelets were being consumed in intravascular coagulation. Cases of both experimentally induced and naturally occurring falciparum, vivax, and ovale malaria were investigated by Shulman *et al.* (1970), who were unable to confirm such coagulation defects despite a consistent fall in the platelet count. They noticed that it was at its lowest at the time of maximum parasitaemia, and drew attention to the considerable evidence in favour of an immunological response modifying the parasite density. They felt that the thrombocytopenia was immunologically mediated. They also produced evidence that the spleen was responsible for removing platelets from the circulation.

In view of our random local observations and the conflicting views in the literature we decided to undertake a prospective investigation into naturally occurring malaria, as it presented at the British Military Hospital, Singapore. Regular platelet counts were made in every case from the time of diagnosis until normal levels were reached. In addition, further investigations were carried out, within local resources, to help clarify the pathogenesis of the thrombocytopenia.

British Military Hospital, Singapore

P. J. BEALE, M.B., B.CHIR., M.R.C.P., Senior Specialist in Medicine (Present address: Royal Army Medical College, London S.W.1)

J. D. CORMACK, M.B., CH.B., F.R.C.P., Consultant in Medicine (Present address: Anzuk Hospital, Changi, Singapore)

T. B. N. OLDREY, M.B., B.S., Trainee in Medicine (Present address: British Military Hospital, Hong Kong)

Method

Thirty-three patients (30 males and three females) aged 13 to 40 years were studied between October 1970 and April 1971. Two of the females were of Malay nationality and one was British. The nationalities of the males were: 15 British, 9 Gurkhali, 3 Malay, and 3 from New Zealand.

Eight of the total had falciparum malaria, 24 had vivax malaria, and one had a mixed infection. All had recently been in malarious zones in South-East Asia, mainly in West Malaysia. All were aware of the protection afforded by the diguanide drug proguanil hydrochloride (Paludrine) 100 mg daily, which is the recognized antimalarial prophylatic used by the British Army in the Far East, and most of them had taken proguanil to a greater or less extent before admission. Usually it was not difficult to obtain confirmation that the drug had been taken irregularly.

An estimation was made of the incubation period of the disease in each patient. On examination the degree of fever and the size of the spleen on full inspiration were noted. A record was kept of the presence or absence of haemorrhagic manifestations and Hess's test was performed.

Diagnosis of the malaria was made by blood film, both thick (Field's stain) and thin (Leishman's stain). The parasite density was recorded by counting the number of parasites per white blood cell (W.B.C.). This was correlated with the W.B.C. count and the result expressed as parasites per cubic millimetre (mm^3). The level of haemoglobin (g/100 ml) was measured and the blood film searched for reticulocytes. Platelets were examined morphologically and the count expressed per mm^3 of blood. In each patient the prothrombin time was measured with Simplastin and the fibrinogen index with Fibrindex and a Coombs test was performed.

Bone marrow was aspirated in eight cases to assess, in particular, the quantity and morphology of the megakaryocytes.

Immunoglobulin IgG, IgA, and IgM levels were measured by a method modified from Mancini *et al.* (1964) in 13 patients both before treatment and between the 10th and 14th days. These 13 patients were the last to present chronologically and, as they seemed to differ in no obvious way from the remainder, were representative of the whole. A third reading was obtained from 5 of these 13 after one month.

Repeated estimations of parasite density, platelet count, haemoglobin, and W.B.C. count were made during treatment and usually until normal values had been reached.

The coagulation tests were repeated if they were originally abnormal on first testing, if the patient developed haemorrhagic manifestations, or if the malaria relapsed.

The plasma acid phosphatase was measured in five patients as a result of a suggestion made by Hill *et al.* (1964), quoting Oski *et al.* (1963), that the platelet destruction caused a raised circulating level of this enzyme.

Course and Treatment

All patients were treated within 24 hours of diagnosis—that is, on Day 0. The 24 patients with vivax malaria received a three-

day course of chloroquine (10 mg of chloroquine base per kg for the first two days, and 5 mg/kg on the third day (W.H.O., 1967; McKelvey *et al.*, 1971)), and primaquine 7·5 mg twice daily for 14 days. There were no relapses. Seven of the eight patients with falciparum malaria were immediately given a dose of two tablets of Darafan (each tablet containing pyrimethamine 25 mg and sulphormethoxine 500 mg). One of these relapsed on the sixth day with a low parasite density of 882/mm³; he was given quinine intravenously (300 mg immediately and followed by 650 mg eight-hourly for two days) followed by oral quinine (650 mg eight-hourly for 12 days).

The eighth patient with falciparum malaria received both Darafan (two tablets immediately) and a three-day course of chloroquine (dosage as above for vivax malaria). He was one of the earlier patients, before it was decided to abandon chloroquine for the treatment of the first attack of falciparum malaria—a decision taken in the context of the prevalence of chloroquine-resistant falciparum malaria, which is reported elsewhere (McKelvey *et al.*, 1971). He relapsed on Day 30 with a low parasite density of 592/mm³ and responded to a five-day course of chloroquine (900 mg on the first day, 600 mg on the second, and 300 mg on the third to fifth days).

One patient had a mixed vivax and falciparum infestation. He received chloroquine and primaquine for the former, and Darafan for the latter, in the same dosages as if he had separate infestations.

All eight patients with falciparum malaria were given primaquine 7·5 mg twice daily for three days before leaving hospital to clear them of gametocytes.

Results

CLINICAL PICTURE

Most patients admitted to a short preceding illness of up to five days' duration, though two had had a short febrile illness a month beforehand, possibly due to malaria. Intermittent fever was the most common presentation. No correlation could be found between the length of the preceding illness and the severity of illness, spleen size, parasite count, or thrombocytopenia. Attempts to estimate the incubation period of illnesses were made, but were clearly so inaccurate that they have not been regarded as of sufficient value to record.

The character of the febrile illness was unremarkably typical of acute malaria. The spleen, however, was palpable in only 19 of the 33 patients, and its size seemed to bear no relation to the length of preceding illness, severity of illness, parasite count, or thrombocytopenia.

HAEMORRHAGIC MANIFESTATIONS

Only one patient had haemorrhagic manifestations. He had falciparum malaria with an initial parasite density of 2,820/mm³, and on the fifth day he developed a large subconjunctival haemorrhage. He was the only patient to have a positive Hess test, which remained positive from the fourth to the sixth day inclusive, and he developed the most profound thrombocytopenia of any patient, the platelet level on the fourth day falling to 11,000/mm³. He was the patient who relapsed on the sixth day.

PLATELETS

If the lowest normal platelet count is taken as 160,000/mm³, then 32 of the 33 patients at some time had thrombocytopenia, with a platelet count of 110,000/mm³ or below, during the course of their illness. In all but one of these 32 patients the lowest reading was reached within the first five days of treatment. Haematological complications would normally be expected to occur below a platelet density of 60,000/mm³. Seventeen patients in this series fell into this category and yet only one showed signs of haemorrhage (see above), his platelet count falling to 11,000/mm³. The platelet levels at different periods of time from the day of diagnosis (Day 0) are given in Fig. 1. It clearly shows a relatively constant level of thrombocytopenia up to the fourth day of treatment (Day +4), and thereafter a gradual rise until all but seven patients had over 160,000 platelets/mm³ by Day +28.

Morphologically the platelets were regarded as normal. This is consistent with the bone marrow findings reported below.

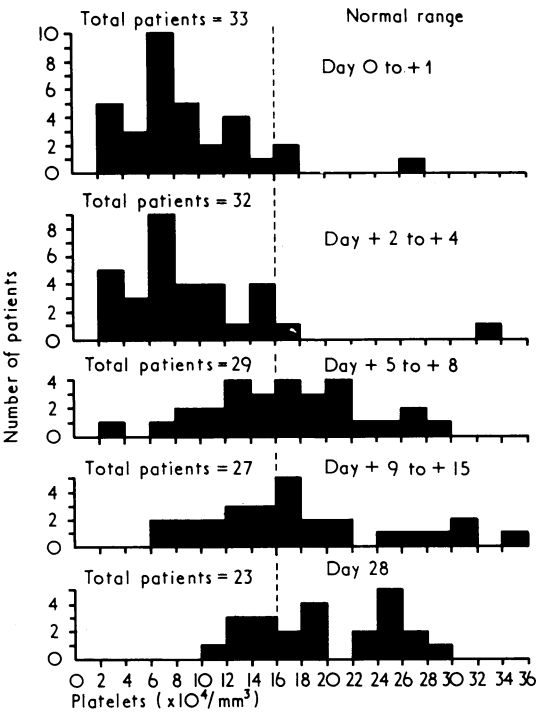

FIG. 1—Platelet levels shown at different periods of time in relation to treatment. (In the case of there being more than one estimation per patient, the average level has been taken.) The total number of readings falls with the passage of time, as repeated platelet estimates were not made in those patients whose levels had already returned to normal.

The fall in platelets occurred in both vivax and falciparum malaria alike. The subsequent rise was coincident with treatment and the disappearance of parasitaemia, but there was no overall correlation between the severity of the thrombocytopenia and the parasite density, haemoglobin concentration, white cell count, length of preceding illness, or size of spleen.

OTHER COAGULATION TESTS

The prothrombin times, Fibrindex tests, and Coombs tests were essentially normal in every patient. The prothrombin time was prolonged by 2 seconds in two patients and by 1 second in three others. These results are not regarded as significantly abnormal.

HAEMOGLOBIN

The initial haemoglobin level ranged from 10 to 17 g/100 ml. In 19 of the 33 patients it remained constant throughout their stay in hospital—in six there was a drop of 1 g, in five a drop of 2 g, in two there was a rise of 1 g, and in one a rise of 2 g/100 ml.

RETICULOCYTES

Apart from a single instance no reticulocyte count was found greater than 3% at any time. The exception was a patient who

had congenital spherocytosis and a constant reticulocytosis between 8 and 12%. She is mentioned below.

WHITE BLOOD CELLS

The initial W.B.C. count ranged from 1,100 to 8,900/mm³, with an average of 4,800. Leucopenia was undoubtedly present in some patients but was not an invariable finding. The polymorphonuclear leucocytes were depressed relatively more than the mononuclears. There was no relation between the total counts and the severity of the illness, degree of parasitaemia, platelet count, or haemoglobin concentration.

PARASITE DENSITIES

Normally more interest is taken in the parasite densities of falciparum malaria patients than of those with vivax malaria, as treatment is influenced. But in this study parasite densities were measured in vivax malaria patients as well. In the eight patients with falciparum malaria the initial density ranged from 81,000 to 480/mm³. The figure of 81,000/mm³ is equivalent to under 2% parasitization of all the red cells. It can be seen that none of these patients with falciparum malaria was heavily infested, as only a level of 150,000/mm³ (about 3% parasitization of red cells) or more is normally regarded as severe enough to require immediate parenteral quinine (McKelvey, personal communication; Beale and Coni, 1970).

The parasite densities in the vivax malaria patients ranged from 23,450 to 120/mm³. Unfortunately in five instances no parasite density was recorded.

All of the 31 patients treated without subsequent relapse were free of parasites by the fourth day. The two who did relapse were free of their parasitaemia by the third day of their initial attack and also by the third day of their treated relapse. It is re-emphasized that no relation could be found between the parasite densities and the depth of thrombocytopenia.

The effectiveness of treatment was shown by the consistent, rapid clearing of parasites from the blood. The haematological results are therefore based on cases of successfully treated and naturally occurring malaria.

IMMUNOGLOBULINS

Significant abnormalities were not detected in the values of immunoglobulins IgG and IgA throughout the illness. But a rise in immunoglobulin IgM was found between the day of diagnosis and the tenth to fourteenth days of treatment in all 13 patients in whom it was measured (see Fig. 2). The normal values for IgM by this method are from 50 to 150 mg/100 ml. At the time of diagnosis five patients with vivax malaria, two with falciparum, and the one with mixed infestation had values within the normal range, but four patients with vivax and one with falciparum malaria already had raised levels. The mean pretreatment level was 162 mg/100 ml, whereas the mean reading between the tenth and fourteenth days was 281 mg/100 ml, a rise of 73%. This must be considered to be a direct response to plasmodial infestation, though the figure of 73% does not reflect the extent of the reaction as 5 of the 13 patients had raised initial levels. They had probably already started to respond. This would be consistent with further observations, made in five patients in whom a third reading of IgM was measured at about the twenty-eighth day, showing a tendency for it to return to its original level. But there are insufficient numbers to allow a definite conclusion to be drawn.

No correlation could be found between the IgM levels—either initial or later values, or the proportionate rise between the two—and the duration of illness before treatment, the degree of parasitaemia, the size of the spleen, or the level of the platelets.

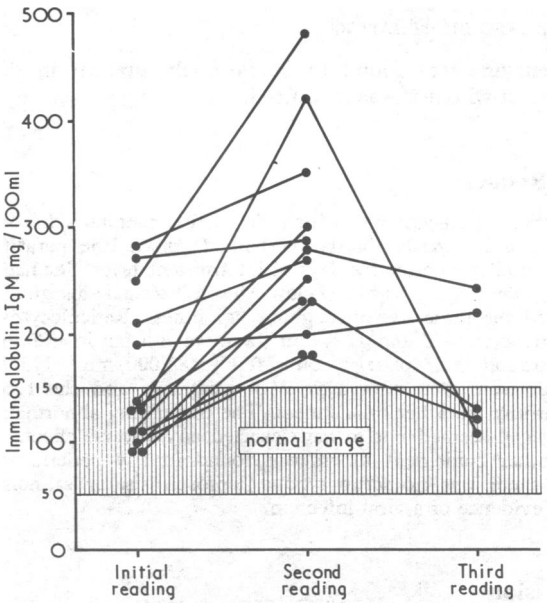

FIG. 2—Changes in immunoglobulin IgM levels in acute malaria. Initial readings were taken at the time of diagnosis, second readings between Day 10 and Day 14 of treatment, and third readings at about Day 28 of treatment.

BONE MARROW EXAMINATION

A bone marrow examination was performed on eight patients. One of them had his marrow examined on the sixth day of treatment (Day +6). He had clinically relapsed on the fifth day, but no parasites were found in his blood. His marrow was therefore aspirated diagnostically as it has been shown that parasites can appear in the marrow before they are demonstrable in the blood (Thomas *et al.*, to be published). Trophozoites and gametocytes of *Plasmodium falciparum* were found, confirming the clinical relapse. Parasitaemia was found later the same day. Marrow aspirations were performed on the other seven patients before treatment. Each patient had the nature of the investigation explained to him, understood that the test was being done for research purposes, and volunteered to assist us.

In all eight cases there was good cellularity and normoblastic erythropoiesis. In the white cell series two patients showed plasma cells in excess, and of a further three patients one showed an increase in monocytes, one showed atypical lymphocytes, and the third showed mild eosinophilia. The megakaryocytes were normal in number and quality in seven patients but in the eighth they were present in excess (0·2% of all nucleated cells) and some promegakaryocytes were seen (Fig. 3). The iron stores were diminished in one or two instances, but generally there was adequate iron. Plasmodial parasites were invariably seen.

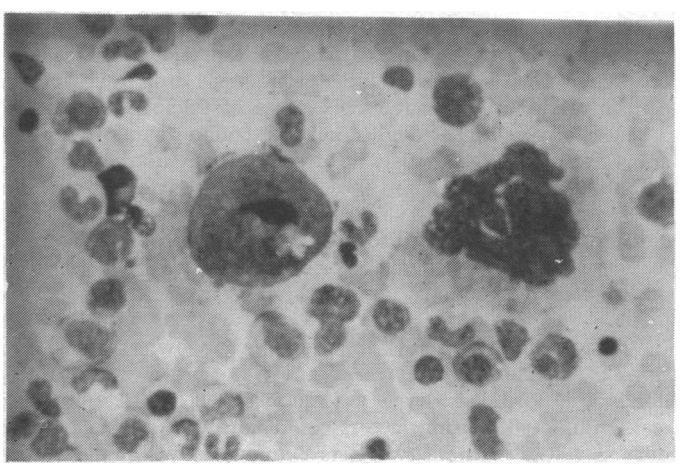

FIG. 3—Bone marrow aspirate from Case 14, showing promegakaryocyte.

PLASMA ACID PHOSPHATASE

This enzyme was found to be normally present in the five patients in whom it was measured.

Case Report

One patient, a 14-year-old British girl, had congenital spherocytosis. She had a low-grade infestation with *P. vivax*, the parasites not being found until after six days of intermittent fever. She had a firm spleen, two fingerbreadths below the left costal margin, which remained the same size throughout her illness. Reticulocytosis was constant between 8 and 12% but there was no fall in haemoglobin concentration. Her platelet count fell to 88,000/mm³. No further parasites were seen after Day 2 of treatment and she recovered uneventfully from her mild illness. The underlying abnormalities of the red cell seemed not to have exerted any adverse effect.

No other coincident illness was found in any patient. In particular there was no scrub typhus, leptospirosis, or salmonellosis, and no evidence of a viral infection.

Discussion

Thrombocytopenia was found in 32 out of 33 malarial patients studied in this series. The lowest platelet levels occurred between the day of diagnosis and the fourth day of treatment. Thereafter there was a rise to normal levels, only four patients having a platelet count below 150,000/mm³ by Day 28, and none below 110,000. Apart from the clinical illness and presence of parasitaemia, no other factors could be found to correlate with the incidence and depth of the thrombocytopenia, and, indeed, recovery of the platelets seemed to be correlated only with the recovery from the illness.

The mechanism of thrombocytopenia in malaria is still not fully understood. Aspiration of bone marrow from eight patients of this series showed no abnormality or deficiency in the megakaryocytes. There was, if anything, a suggestion of overstimulation, as shown by both promegakaryocytes and an increased number of megakaryocytes in one patient (Fig. 3). This is in agreement with the findings of Shulman *et al.* (1970). It is therefore unlikely that the megakaryocytes are at fault, and bone marrow failure cannot be considered a factor in the development of thrombocytopenia. Shulman *et al.* (1970) also seem to be convinced that the platelets so formed are being released satisfactorily into the circulation.

An entirely different mechanism for the production of thrombocytopenia was postulated by Devakul *et al.* (1966) and by Dennis, Conrad, and their associates (Dennis *et al.*, 1966, 1967; Dennis and Conrad, 1968; Conrad, 1969). They felt that the platelets were being removed from the circulation by consumption in intravascular coagulation, and presented convincing evidence by showing depletion of coagulation factors and the presence of fibrinogen degradation products as well as thrombocytopenia. But Dennis and Conrad's studies were for the most part carried out on experimental malaria in monkeys or on humans with a late relapse of drug-resistant falciparum malaria. Devakul *et al.* (1966) also found a pronounced drop in fibrinogen concentration in two out of six cases of falciparum malaria. Their two patients had higher parasite counts than any of ours and were the most seriously ill of the six patients they studied.

The findings of Shulman *et al.* (1970) are in contrast to those of Dennis *et al.* (1966, 1967). They could find no depletion of clotting factors in their studies of humans with *P. falciparum*, *P. vivax*, or *P. ovale* infections or of monkeys with *P. cynomolgi* or *P. knowlesi* infections, despite the presence of thrombocytopenia.

We confirm Shulman's findings in our own studies. No significant abnormalities were found in the prothrombin times, nor in the fibrinogen levels as demonstrated by the Fibrindex test. Individual clotting factors could not be estimated but the normal values in these two tests eliminate any significant disorder of coagulation.

Furthermore, signs of bleeding occurred only once in the form of a subconjunctival haemorrhage the day after that particular patient's platelet count had fallen to 11,000/mm³, the lowest level attained by any patient.

As haemostasis was so regularly maintained despite gross depletion in the numbers of circulating platelets, those that were present must have been functioning normally. No patient in this series had a parasite density over 81,000/mm³, and it is probable that in more severe *P. falciparum* infections intravascular coagulation can occur. However, we have shown that thrombocytopenia can develop independently of intravascular coagulation and that, in malaria, the demonstration of thrombocytopenia alone cannot be used as a basis for diagnosing intravascular coagulation. It is therefore important to show depletion of clotting factors before making the diagnosis, and before giving the specific but potentially dangerous antidote, heparin.

Removal of presumably normal platelets in malaria by a hypertrophied reticuloendothelial system is supported by the frequent finding of an enlarged spleen and liver, and morphologically there is evidence for the involvement of macrophages in the elimination of parasites, pigment, and erythrocytes. It was surprising, however, to find the spleen palpably enlarged in only 19 of our 33 patients, an experience similar to that of Hill *et al.* (1964), and that its size bore no relation to the severity or duration of the illness, nor to the degree of parasitaemia or thrombocytopenia.

No endotoxin has ever been found to aid the removal of platelets from the circulation, but antimalarial antibodies have been found sufficiently early in the illness (Shulman *et al.*, 1970) to be considered an influence in platelet destruction. We therefore set out to measure the immunoglobulins, particularly the IgM fraction, the rise of which is known to tally closely with the formation of malarial antibody (Tobie *et al.*, 1966). Zuckerman (1969) carefully emphasized that all gammaglobulin is not antibody, and both Curtain *et al.* (1964) and Turner *et al.* (1966) pointed out that raised levels of immunoglobulins can be due to intercurrent infections, but our studies were conducted among previously healthy individuals, and no coincident disease was detected. Hence we felt justified in assuming that changes in immunoglobulin values reflected changes in malarial antibody.

Measurements in 13 cases showed a significant rise in the immunoglobulin IgM during the first two weeks of treatment (Fig. 2). In view of the raised levels at diagnosis and before treatment in five of the cases, the stimulus for production of IgM and, by inference, malarial antibody has been shown to be present before the appearance of parasitaemia. As the thrombocytopenia was most profound at this early stage, between Day 0 and Day +4 of treatment, malarial antibody has to be considered as a factor in the production of the thrombocytopenia.

The level of immunoglobulin IgM seemed to be falling by the twenty-eighth day. This agrees with the conclusions of Abele *et al.* (1965) and Zuckerman (1969), who found the IgM fraction (or its equivalent 19*s* macroglobulin) to be increased towards the beginning of the illness, and that as the IgM level began to fall the immunoglobulin IgG (or its equivalent 7*s* gammaglobulin) began to rise and remained high as a more permanent indication of previous malarial infection. We did not find any noticeable change in the IgG, but our measurements may have been made too early in the course of the illness, and no further conclusions can be drawn.

Quinine has been incriminated as a factor in the pathogenesis of blackwater fever in falciparum malaria, and, not unnaturally, both quinine and other antimalarial drugs have been scrutinized for undesirable haematological side effects.

We conducted a careful inquiry into the drug history of all our patients, and apart from an occasional aspirin taken by two of them for their fever, the only drug frequently taken was proguanil hydrochloride (100 mg daily) as an antimalarial prophylactic. Twelve volunteers taking proguanil hydrochloride 100 mg daily but not suffering from malaria had platelet counts performed—there was no instance of thrombocytopenia. We stress

that 32 out of our 33 patients had developed thrombocytopenia before any other drug was given. The one patient who had a haemorrhage on the fifth day of treatment received Darafan on Day 0, and even he had had thrombocytopenia on admission. Therefore, it is concluded that drugs played no part in the pathogenesis of thrombocytopenia in these patients.

Conclusion

Thrombocytopenia is the rule in the acute attack of malaria, and it is not associated with depletion of other coagulation factors in the mild case. We suggest that the platelets are removed at an excessive rate from the circulating blood, probably by the reticuloendothelial system, and that they are in some way altered immunologically, which assists in their removal.

It must be realized that thrombocytopenia can occur in malaria in the absence of intravascular coagulation, and that heparin should be withheld in such cases until other evidence is produced of disordered coagulation, when its use might then be justified.

We would like to thank Colonel R. M. Vanreenen, late R.A.M.C., Major M. J. G. Thomas, R.A.M.C., and Mr. E. Ellis, all lately of the Far East Command Laboratory at the British Military Hospital, Singapore, for their encouragement and hard work; Brigadier T. P. H. McKelvey, late R.A.M.C., and Colonel W. O'Brien, late R.A.M.C., for many helpful suggestions in the preparation of this paper; and Mrs. Irwin for her secretarial help.

Requests for reprints should be sent to Major P. J. Beale, Royal Army Medical College, Millbank, London S.W.1.

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Cardiovascular Effects of Methylmethacrylate Cement

DOUGLAS J. PEEBLES, RICHARD H. ELLIS, S. D. K. STRIDE, B. R. J. SIMPSON

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Summary

Experiments were carried out on dogs in an attempt to identify the mechanisms underlying the systemic hypotension associated with the application of acrylic cement substances to raw bone surfaces, as in reconstructive hip surgery. Intravenous injection of the liquid component of such cements (monomeric methylmethacrylate) into six dogs produced a significant fall in blood pressure together with an increase in heart rate and cardiac output. This seemed to be due to peripheral vasodilatation caused directly by the monomer and not through the release of histamine. Absorption of free monomer from the mixed cement into the systemic circulation at operation is likely to have the same effect. Precautionary measures can be taken and groups of patients who are especially at risk can be identified, thus reducing the hazards of total hip replacement.

Department of Anaesthesia and the Anaesthetic Unit, the London Hospital, London E1 1BB

DOUGLAS J. PEEBLES, M.B., B.S., F.F.A.R.C.S., Senior Registrar (Present appointment: Consultant Anaesthetist, Sydenham Children's Hospital, London S.E.26, and Bromley Hospital)
RICHARD H. ELLIS, M.B., B.S., F.F.A.R.C.S., Lecturer (Present appointment: Consultant Anaesthetist, St. Bartholomew's Hospital, London EC1A 7BE)
S. D. K. STRIDE, D.A., F.F.A.R.C.S., Consultant Anaesthetist
B. R. J. SIMPSON, D.A., F.F.A.R.C.S., Professor

Introduction

Several operations for the reconstruction of diseased hip joints involve the insertion of prostheses fixed in position with acrylic bone cement. These cements consist of two components, a liquid and a powder, which are mixed shortly before use. The mixture sets hard in 5 to 10 minutes, considerable heat being generated in the process (Homsy, 1969; Charnley, 1970; Frost, 1970; Jefferiss, 1971). The basis of the acrylic cements is methylmethacrylate, which can exist either in a liquid (monomeric) or a solid (polymerized) phase. The powdered component differs somewhat in the two commercially available cements (C. M. W. Bone Cement; Surgical Simplex-P) but consists essentially of methylmethacrylate in granular form and benzoyl peroxide, which serves as a coactivator. In both preparations 99·9% of the liquid component consists of methylmethacrylate monomer, the remainder being made up of water, methanol, methacrylic acid, dimethylparatoluidine (another coactivator), and hydroquinone (which prevents spontaneous polymerization). The mixing together of the liquid and the powder brings about the polymerization of the liquid monomer, which then binds together the previously polymerized powder (Charnley, 1970).

Recent reports have suggested that systemic hypotension may follow the application of the mixed cement to the raw bone surfaces (Frost, 1970; Harris, 1970; Hyland and Robins, 1970; Ling and James, 1971; Michelinakis *et al.*, 1971; Phillips *et al.*, 1971; Thomas *et al.*, 1971). The fall in blood pressure is usually transient; Charnley (1970) stated that hypotension "presents itself to a noticeable degree in less than a third of cases and always the blood pressure recovers its normal levels within 3-5 minutes." However, Powell *et al.* (1970) recorded two cases of cardiac arrest associated with the use of acrylic cement, and we ourselves have experienced one fatality occurring during an