Lietman and Bywaters (1963). Clinical diagnosis was established in 20 (7%) of a series of 285 cases. Common concomitant features were a skin rash, lymphadenopathy, splenomegaly, pulmonary disease, and amyloid disease. The clinical course of this form of pericarditis is usually short and of a benign nature.

A further form which merits mention in the present context is allergic pericarditis. Clarkson, McCredie, and Fleischl (1964) describe an example in which extensive urticaria was associated with clinical evidence of pericarditis and with characteristic E.C.G. changes ; signs of a pericardial effusion were also evident in the *x*-ray picture. Treatment consisted in antihistamine and symptomatic drugs, and recovery was complete. The pericardium must be considered as a structure in which allergic phenomena may occur (Wolff and Grunfeld, 1963). Recognition of the concept of drug-induced and hypersensitivity reactions in the aetiology of pericarditis may help to identify some of the 50% or so of those cases of pericarditis that are labelled " idiopathic."

Summary

In the elucidation of pericarditis of undetermined origin the possibility of a drug-induced state merits consideration. This and other forms of iatrogenic pericarditis are reviewed. The report of an example attributed to phenylbutazone administration is presented ; corticosteroid therapy appeared to be life-saving. Differentiation from the pericarditis of rheumatoid disease is emphasized. Allergic pericarditis is a distinct entity.

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Preliminary Communications

Increased Platelet Adhesiveness in Recurrent Venous Thrombosis and Pulmonary Embolism

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The relation between platelet adhesiveness and thrombosis has been the subject of considerable investigation (see review by O'Brien, 1964). Studies directed towards venous thrombosis have been few and have been limited to the acute phase of the disease. The present investigation has revealed a significant and apparently persistent increase in platelet adhesiveness in patients with recurrent venous thrombosis and in patients with recurrent pulmonary embolism.

Patients Studied

Platelet adhesiveness was measured in nine patients and 20 control subjects. The patient's ages ranged from 26 to 65, with a mean of 45.3 years, and the ages of the control subjects ranged from 23 to 78, with a mean age of 41.3 years. A diagnosis of idiopathic recurrent venous thrombosis, recurrent pulmonary embolism, or thromboembolic pulmonary hypertension had been made in the patients (see Table II). Repeated estimations of platelet adhesiveness were performed during the quiescent stage of the disease when there were no clinical signs of active thrombophlebitis.

The control subjects were 12 healthy members of the laboratory staff and eight hospital in-patients who showed no clinical evidence of vascular disease. Screening tests for fibrinolytic inhibitors were performed on five patients and five healthy control subjects.

Materials

Glass beads (Reflex Perlen), 0.5 mm. in diameter, were prepared as described by Hellem (1960). Portex tubing (Portland Plastics Ltd., Kent) N.T.13, internal diameter 0.217 in. (0.55 cm.), was used in the preparation of the glass bead columns. Bovine thrombin (S. Maw and Sons Ltd., England) was dissolved in equal parts of glycerol and saline to a concentration of 100 units/ml. and stored at −20° C. Human urokinase (Leo Laboratories Ltd., London) was dissolved in 0.5% gelatin in phosphate buffer 0.1 M *p*H 7.6, stored at −20° C., and thawed immediately before use. Human plasmin was obtained from spontaneously activated plasminogen in 50% glycerin (Kabi Pharmaceutical Ltd., London) and stored at 4° C. Fibrin plates were prepared from bovine fibrinogen (Armour Pharmaceutical Company Ltd., England) by the method of Müllertz (1952) as modified by Alkjaersig *et al.* (1959).

Methods

Blood for the study of platelet adhesiveness was collected into disposable plastic syringes and mixed in plastic tubes with 3.1% sodium citrate (one part citrate to nine parts of blood). The packed cell volume was measured and an adjustment was made to the patient's blood to bring this value to 40%, either by the addition of high-spun plasma (if the reading was >45%) or packed red cells (if the reading was <35%). The blood was allowed to stand at room temperature (19–21° C.) and was tested 30 to 60 minutes after collection.

Platelet adhesiveness was measured at room temperature by a modification of the method orginally described by Hellem (1960). Two millilitres of citrated blood was passed at a constant rate through a column (6 cm. in length, containing 2.5 g. of glass beads) by means of a motor-driven 2-ml. disposable plastic syringe. The initial studies were performed with 5-g.

columns and with platelet-rich plasma with added adenosine diphosphate, as well as with citrated whole blood. The whole-blood technique was found to be more reliable, and the 2.5-g. columns were found more sensitive for detecting increased adhesiveness. The blood was in contact with the glass beads for 26 ± 1 second. Platelet counts were performed before and after the passage of the blood through the column by the method of Brecher and Cronkite (1950). The percentage decrease in platelet count after the passage of the blood through the column is taken to be a reflection of platelet adhesiveness.

High-spun plasma for fibrinolytic studies was prepared from citrated blood by centrifugation at 2,000 *g* for 30 minutes in an M.S.E. refrigerated centrifuge at 4° C. The plasma was kept at 4° C. and tested within two hours of collection.

Urokinase sensitivity tests were performed by the addition of urokinase to an equal volume of plasma, and the mixture was immediately tested for anti-urokinase activity: (*a*) by recording the lysis time after clotting 0.2-ml. aliquots of the plasma mixture with 0.1 ml. of thrombin (10 unit/ml.); and (*b*) by pipetting 0.03-ml. aliquots of the plasma mixture on to a fibrin plate and recording the area of lysis after 18–24 hours' incubation at 37° C. Three concentrations of urokinase were used, producing final concentrations of 50, 37.5, and 25 Leo units/ml. of plasma. Each estimation was performed in duplicate on the patient and control plasma.

Anti-plasmin assays were performed by substituting plasmin for urokinase in the test systems described. Two concentrations of plasmin, giving final concentrations of 5 and 7.5 casein units/ml. of plasma, were used. Each estimation was performed in duplicate on patient and control plasma.

Results

The packed cell volume was greater than 45% in one patient (Case 8) who had thromboembolic pulmonary hypertension and less than 35% in one hospital control (No. 14). In each instance the packed cell volume was adjusted to approximately 40% before platelet adhesiveness was measured.

Data on the control subjects are summarized in Table I. The platelet count was within the normal range in all subjects. Platelet adhesiveness was measured on a number of occasions in some of the healthy controls and on one occasion only in each hospital control. There was no significant difference in platelet adhesiveness between the healthy and hospital controls ($P>0.1$) or between males and females within the groups ($P>0.1$). There was no significant correlation between platelet adhesiveness and age ($P>0.1$).

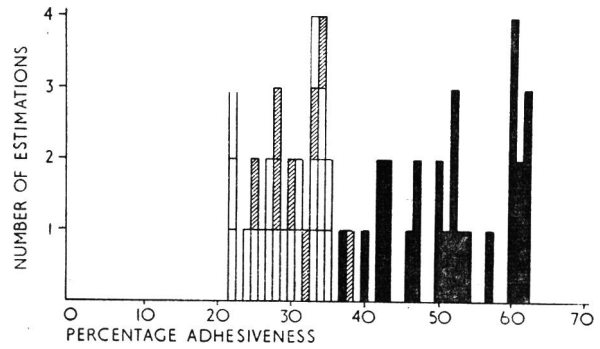
The data on patients with thromboembolic disease are summarized in Table II. The platelet count was just above the upper limit of normal in one patient (Case 3). As in the control subjects, there was no significant correlation between age and adhesiveness ($P>0.1$). The Chart shows the distribution of platelet adhesiveness in healthy controls, hospital controls, and patients with thromboembolic disease. Every estimation carried out on each individual is recorded. Platelet adhesiveness was significantly greater in the patients than in the control groups ($P<0.001$).

TABLE I.—*Platelet Adhesiveness Studies on Normal and Hospital Controls*

No.	Age and Sex	No. of Observations	Platelet Count (10^3/c.mm.)		Adhesiveness (%)		Clinical Description
			Range	Mean	Range	Mean	
1	33 M	5	150–200	176	22–35	28	Normal
2	65 F	1		328		27	,,
3	45 M	2	224–256	240	31–35	33	,,
4	30 M	4	238–296	273	22–31	27	,,
5	29 F	2	194–220	207	24–27	26	,,
6	45 F	1		160		25	,,
7	30 M	1		250		34	,,
8	27 F	1		200		22	,,
9	60 F	2	255–256	255·5	33–34	33	,,
10	45 M	1		169		31	,,
11	26 F	1		264		33	,,
12	23 F	1		185		34	,,
13	78 M	1		227		32	Carcinoma of stomach
14	30 F	1		170		38	Pregnant. Epilepsy
15	40 M	1		330		30	Factor VIII deficiency
16	60 M	1		210		33	Hypertension. Chronic bronchitis
17	39 F	1		180		28	Rheumatic heart disease
18	61 F	1		380		34	Empyema
19	36 M	1		200		25	Pneumothorax
20	50 F	1		175		28	Hypertension

TABLE II.—*Platelet Adhesiveness Studies on Patients With Recurrent Venous Thrombosis, Pulmonary Embolism, and Thromboembolic Pulmonary Hypertension*

Case No.	Age and Sex	No. of Observations	Platelet Count (10^3/c.mm.)		Adhesiveness		Clinical Description
			Range	Mean	Range	Mean	
1	52 M	4	170–200	182	40–47	43	Recurrent venous thrombosis in legs and arms
2	45 M	1		133		37	Recurrent venous thrombosis
3	43 M	3	370–480	425	42–50	44	Recurrent venous thrombosis in legs. Superficial venous thrombosis in arms
4	43 F	2	360–390	375	43–61	52	Deep venous thrombosis. Thrombosis of superior and inferior vena cava
5	35 F	5	169–184	180	51–62	54	Pulmonary embolism followed by deep venous thrombosis
6	36 F	2	172–174	173	47–52	48	Recurrent venous thrombosis. Recurrent pulmonary emboli
7	65 M	1		298		46	,, ,, ,, ,,
8	63 M	2	173–190	181·5	60–60	60	Recurrent venous thrombosis. Recurrent pulmonary emboli. Thromboembolic pulmonary hypertension
9	26 F	9	148–247	177	50–62	55	Thromboembolic pulmonary hypertension



Distribution of platelet adhesiveness in healthy controls (□), hospital controls (▨), and patients with thromboembolic disease (■). Platelet adhesiveness is significantly greater in the patients than in the control groups ($P<0.001$).

Tests for Fibrinolytic Inhibitors.—Five patients (Cases 1, 3, 6, 8, and 9) were screened for plasma anti-urokinase and anti-plasmin activity. In each case there was no significant difference in inhibition of fibrinolytic activity between patient and control plasma.

Discussion

The present investigation has revealed a significant increase in platelet adhesiveness in patients with recurrent venous thrombosis, recurrent pulmonary embolism, and thromboembolic pulmonary hypertension. The studies do not distinguish between a platelet factor or a plasma factor as the cause of the increased platelet adhesiveness. In addition, no firm conclusions can be drawn as to whether the increase in platelet adhesiveness is the cause or the consequence of the recurrent thrombotic or thromboembolic episodes. Platelet adhesiveness is increased in post-operative and post-partum states (Wright, 1942), a finding which suggests that in some circumstances at least it may contribute to the initial development of venous thrombosis. On the other hand, platelet adhesiveness has been found to be elevated in active thrombophlebitis and to return to normal

when activity subsides (Bobek and Čepelák, 1958). This finding suggests that the increase in platelet adhesiveness observed here might be a consequence of endothelial disease or of continuing thrombosis rather than the cause of the recurrent thromboembolic episodes. However, whether cause or consequence, it seems reasonable to assume that an increase in platelet adhesiveness might contribute to the progression of the underlying thrombotic process and interfere with the re-establishment of normal venous patency.

The mechanism by which continuing or incompletely resolved venous thrombosis might increase platelet adhesiveness is not readily apparent. Murphy and Mustard (1962) reported increased platelet turnover in atherosclerosis and noted that in these patients there was an increase in platelet adhesiveness. It is possible that platelet turnover is also increased in chronic or recurrent venous disease and that the increase in platelet adhesiveness observed in our patients is a consequence of the presence of a relatively young platelet population.

The pathogenesis of idiopathic recurrent venous thrombosis is obscure. Treatment with oral anticoagulants does not appear to be as effective in reducing the number of thromboembolic episodes as in post-traumatic and post-operative venous thrombosis (Sevitt, 1962). In addition, the increase in platelet adhesiveness appears to persist between overt thrombotic or thromboembolic episodes. In keeping with previous observations (Hellem, 1960) platelet adhesiveness did not appear to be influenced by treatment with oral anticoagulants.

Other factors may be implicated in the pathogenesis of recurrent venous thrombosis. Spittel *et al.* (1960) reported accelerated thromboplastin generation in a proportion of patients with idiopathic recurrent venous thrombosis, and Nilsson *et al.* (1961) demonstrated a marked increase in fibrinolytic inhibitor activity in one patient with recurrent venous thrombosis. We were unable to find evidence of a significant increase in anti-urokinase or anti-plasmin activity in the patients studied. It is likely that the observed increase in platelet adhesiveness is but one of a number of factors which are important in the pathogenesis of "idiopathic" recurrent venous thrombosis and thromboembolic pulmonary hypertension. The present findings are of particular interest because they would lead to a possible therapeutic approach to the problem. Investigations are currently in progress to explore the therapeutic possibilities of agents which have been reported to reduce platelet adhesiveness.

SUMMARY

Platelet adhesiveness was found to be increased in nine patients with either recurrent venous thrombosis or recurrent pulmonary embolism. The significance of these observations is discussed.

We are grateful to the consultant staff of Hammersmith Hospital for permitting us to study patients under their care. We wish to thank Professor J. V. Dacie for his helpful comments and Miss I. Leets for assistance with the preparation of the chart.

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Medical Memoranda

Pure Neural Tuberculoid Leprosy

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In the literature on leprosy there is scant reference to leprosy of a pure neural tvpe (nerve involvement without skin lesions), and there are probably several reasons for this. First, patients in the tropics tend to ignore early symptoms of peripheral nerve damage ; secondly, it is not generally appreciated by the medical profession that leprosy is primarily a neurological disease, hence pure neuritic leprosy is likely to be overlooked or misdiagnosed ; and, thirdly, even when primary neural leprosy is suspected, nerve biopsy is usually impracticable One of us (Jopling, 1956) has reported a case of borderline (dimorphous) leprosy which remained purely neural for eight years and in which nerve biopsy showed a typical borderline histology, but in our search of the literature we have not been able to find a report in which a pure neural form of tuberculoid leprosy has been proved. Hargrave and Marion (1964) reported a case of leprotic involvement of multiple peripheral nerves in the absence of skin lesions, and, judging by the number of nerves involved and the microscopical appearances on nerve biopsy, this was another example of pure neuritic borderline leprosy. A lepromin test was not carried out on this patient. On the subject of pure neural tuberculoid leprosy Cochrane and Davey (1964) state that this type of leprosy is theoretically possible and that primary neuritic cases are occasionally encountered in which the lepromin test is strongly positive. But they admit that no case has been proved by nerve biopsy, and add: "So far any nerves which have shown a tuberculoid histology have come from cases in which there have also been visible cutaneous manifestations." We consider it important that the existence of this form of tuberculoid leprosy should be established beyond doubt, not only to satisfy leprologists who may have doubted its validity but also to draw the attention of neurologists to this clinical entity. This necessitates a nerve biopsy. The lepromin test is not enough, for it is a non-specific test, and though it is always positive in tuberculoid leprosy it may equally be positive in healthy persons.

CASE REPORT

An Anglo-Indian man, aged 38, was born in Hyderabad and came to England in October 1961. He worked as a van driver, and