CHANGES IN BLOOD AFTER USING AN EXTRACORPOREAL CIRCULATION

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Important haematological changes have been reported after the use of an extracorporeal circulation for open cardiac surgery. Brown and Smith (1958) have summarized the changes which may lead to a haemorrhagic tendency; these include inadequate neutralization of heparin, thrombocytopenia, development of increased fibrinolytic tendency and fibrinogenopenia, alteration of coagulation factors, and development of circulating anticoagulants. With refinement of apparatus and technique these complications have become less frequent but continue to be reported.

This paper records further observations on changes occurring in the coagulation mechanism and white cells in a series of 13 patients subjected to open cardiac surgery using an extracorporeal circulation. The patients, all suffering from congenital heart disease, were taken at random from a larger series undergoing surgery at the General Infirmary at Leeds between December, 1958, and November, 1959.

Methods

The extracorporeal circulation consisted of a Melrose (1953) oxygenator together with an occlusive pump (Nixon, 1959), and hypothermia was not used. Before perfusion 2.5 mg./kg. body weight of heparin was injected intravenously and 20 mg. of heparin was placed in each bottle of donor blood. In this series fresh donor

TABLE I.—Duration and Rates of Perfusion

Case	Sex	Age in Years	Duration of Perfusion (Minutes)	Perfusion Rates (ml. kg. min.)
1	F	34	43	73
2	F	23	47	66
3	F	16	24	73
4	F	7	29	109
5	M	16	19	80
6	F	25	35	68
7	F	11	36	96
8	F	12	40	82
9	F	14	25	78
10	F	29	20	55
11	M	16	22	72
12*	F	5	—	—
13	F	22	27	80

* Died on perfusion.

blood was obtained just before operation and collected into siliconed glass bottles. At the conclusion of perfusion protamine sulphate was injected according to titration (Perkins *et al.*, 1956) and repeated as necessary. The duration of perfusion varied from 19 to 47 minutes and the rate from 56 to 109 ml./kg. body weight per minute. Table I summarizes the age and sex of the patients, together with the duration and rates of perfusion.

Siliconed syringes and chemically clean glassware were used throughout. Blood for haematological examination was generally taken between 10 a.m. and 11 a.m. on the day before operation (pre-operative), just before beginning perfusion and before heparinization (pre-perfusion), after perfusion just after protamine had been

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given (post-perfusion), at the end of the operation (post-operative), and between 10 a.m. and 11 a.m. on the day after the operation (first day). The effects of any diurnal variations would thus be approximately the same for each patient.

Cell Counts.—These were performed on blood taken into siliconed tubes containing the dipotassium salt of E.D.T.A. (ethylenediamine tetra-acetic acid) as anti-coagulant. The absolute number of various white cells were calculated from total and differential counts.

Coagulation Studies.—Blood was collected into siliconed tubes containing one part of 3.8% w/v trisodium citrate to nine parts of blood. Platelet-poor plasma was obtained by centrifuging at 3,000 r.p.m. for 30 minutes. Thrombin times were performed according to the method of Biggs and Macfarlane (1957) with and without toluidine blue (50 mg./100 ml. in 0.9% saline). One-stage prothrombin times, two-stage prothrombin estimations, and thromboplastin generation tests were carried out as described by Biggs and Macfarlane (1957). Antihaemophilic globulin (A.H.G.) assays were performed by the method of Pitney (1956). Thrombin times and one- and two-stage prothrombin tests were performed within three hours of sampling. Plasma and serum for other tests were stored in siliconed tubes at -20°C ., but in no case did more than two days elapse before testing.

Fibrinogen and Fibrinolysis

Blood was taken into tubes containing dried potassium oxalate at a concentration of 2.5 mg./ml. Plasma was obtained by centrifuging at 3,000 r.p.m. for 10 minutes.

Plasma fibrinogen was estimated by the method of King (1951).

Fibrinolysis.—A euglobulin lysis time method was found to be convenient, and is described in detail. A similar technique was described by von Kaulla and Schultz (1958) and by Buckell (1958). To 9 ml. of distilled water was added 0.5 ml. of plasma, followed by 0.1 ml. of 1% acetic acid to bring the pH to 5.2. The euglobulin was allowed to precipitate at 4°C . for 30 minutes, and the precipitate was collected by centrifuging at 3,000 r.p.m. for five minutes. The excess supernatant was removed by draining, and the undisturbed precipitate was washed once with a mixture of distilled water 90 parts, normal saline 5 parts, and sufficient 1% acetic acid to bring the pH to 5.2. The inside of the tube was carefully wiped dry while inverted and the precipitate dissolved completely in 0.5 ml. of veronal-acetate-buffered saline at pH 7.4. The euglobulin solution was placed in a water-bath at 37°C ., and after two minutes clotted with 0.5 ml. of M/40 calcium chloride solution. The tubes were inspected periodically, and the time taken for complete lysis was noted. Each test was set up in duplicate as soon as the blood was taken, and the final stage of clotting was completed one hour after sampling. This precaution was felt to be necessary in view of the reported lability of fibrinolytic enzymes (Fearnley *et al.*, 1952). It was found that close duplication of results could be obtained by this method.

Results

Platelet counts are shown in Table II. A marked fall in platelets followed perfusion in most instances. Moreover, in some there was a further fall by the end of the operation and little evidence of return to normal by the next day. Twelve of the 13 cases developed thrombocytopenia at some stage, 10 while on perfusion.

Only the post-perfusion count was done on the other case (No. 10), and it is possible that this patient also developed thrombocytopenia later.

Purpuric manifestations did not develop in any of the patients.

White-cell counts (Table III) were performed in nine cases. A moderate neutrophil leucocytosis occurred in seven cases after perfusion, but the count tended to fall

TABLE II.—Platelets/c.mm.

Case	Pre-operative	Pre-perfusion	Post-perfusion	Post-operative	First Day
1	198,000	215,000	221,000	101,000	59,000
2	241,000	195,000	105,000	85,000	63,000
3	210,000	200,000	77,000	56,000	101,000
4	325,000	195,000	71,000	103,000	121,000
5	220,000	240,000	180,000	160,000	95,000
6	235,000	240,000	120,000	82,000	99,000
7	210,000	200,000	53,000	92,000	82,000
8	325,000	224,000	130,000	111,000	120,000
9	180,000	—	158,000	148,000	91,000
10	175,000	170,000	176,000	—	—
11	265,000	205,000	165,000	115,000	—
12*	—	160,000	39,000	—	—
13	—	363,000	164,000	—	—

* Died on perfusion.

TABLE III.—White Cells/c.mm.

Case	Polymorphs/ c.mm.			Lymphocytes/ c.mm.			Eosinophils/ c.mm.		
	Pre-perf.	Post-perf.	Post-op.	Pre-perf.	Post-perf.	Post-op.	Pre-perf.	Post-perf.	Post-op.
1	10,400	15,700	4,700	2,900	1,190	616	160	170	150
2	4,600	10,500	7,300	2,700	460	1,100	160	0	80
3	3,800	11,000	5,600	2,200	960	500	0	0	0
4	4,600	8,700	5,200	2,000	1,700	1,300	380	0	0
5	2,000	7,700	4,350	2,700	1,600	800	100	0	0
8	4,470	4,800	8,870	3,300	1,930	1,120	80	70	180
9	—	12,200	15,000	—	1,380	1,180	—	140	0
11	3,000	5,500	5,300	1,400	1,500	1,050	180	0	0
12*	6,500	3,700	—	3,400	3,600	—	100	240	—
Mean	4,920	8,866	7,040	2,575	1,569	958	170	69	51

* Died on perfusion.

by the end of the operation in five of these. The lymphocyte counts showed a more gradual fall and had reached their lowest level by the end of the operation. Although eosinophil counts by the method used are rather inaccurate, there was a tendency for these cells to decrease after perfusion. No correlation could be found between the changes in these counts and the duration or rate of perfusion.

Plasma Fibrinogen and Fibrinolysis (Table IV)

There was a moderate fall in plasma fibrinogen levels after perfusion in 10 out of 13 cases. Of the other three cases, two (Nos. 2 and 3) showed no change and one (No. 11) an increase in fibrinogen levels.

Excess fibrinolysis did not develop before perfusion, but euglobulin lysis times were lower after perfusion

TABLE IV.—Fibrinolysis and Plasma Fibrinogen

Case	Euglobulin Lysis Times (Minutes)				Plasma Fibrinogen (mg./100 ml.)	
	Pre-op.	Pre-perf.	Post-perf.	First Day	Pre-perf.	Post-perf.
1	90	60	80	165	474	370
2	125	120	120	270+	275	281
3	135	120	100	360	264	264
4	80	90	105	330	197	131
5	140	135	100	240	381	337
6	160	160	75	260+	312	264
7	—	100	40	—	499	438
8	160	150	90	330	486	312
9	120	120	60	300	169	65
10	—	195	150	—	406	364
11	100	105	90	270	350	500
12*	—	65	73	—	385	224
13	145	135	57	280	436	319

* Died on perfusion.

in 9 out of the 13 cases, and this change was quite marked and therefore of more significance in five of these (Cases 6, 7, 8, 9, and 13). This indicates enhanced fibrinolysis in these patients developing while on perfusion.

Although no patient developed a haemorrhagic tendency which could be due to excess fibrinolysis or fibrinogenopenia, it is apparent that these changes did occur in some instances.

In contrast to the findings immediately after perfusion, the euglobulin lysis times were strikingly increased on the first post-operative day in every patient tested. These findings suggest a decrease in fibrinolytic enzymes or activators at that time, and are discussed below.

A relationship between fibrinolysis and fibrinogen levels is not apparent in every case. One patient (Case 9) at least did show a tendency for fibrinogen levels to follow euglobulin lysis times over a period of one week after operation (see Chart). This was discovered because

Plasma fibrinogen levels and euglobulin lysis times after repair of two atrial septal defects. The patient was a 14-year-old girl (Case 9).

the low fibrinogen levels after perfusion prompted a more prolonged investigation of this case. The patient was a girl of 14 years who was subjected to a repair of two atrial septal defects. Fibrinolysis developed after perfusion and persisted until the end of the operation. This was accompanied by a fall in fibrinogen levels to 60 mg./100 ml. The next morning the euglobulin lysis time had risen to 300 minutes and the plasma fibrinogen to 324 mg./100 ml. The prolonged euglobulin lysis time persisted on the second post-operative day, when the plasma fibrinogen had risen to 520 mg./100 ml., but one week later both had fallen to near pre-perfusion levels.

Coagulation Studies

It was recognized at an early stage in this investigation that despite the use of a protamine titration some heparin activity may remain in the post-perfusion samples. This has recently been confirmed by Peden and McFarland (1959), who recommend the use of plasma thrombin times to control dosage of protamine. The presence of heparin in some samples rendered the assay of coagulation factors extremely difficult, although not usually leading to excess bleeding in the patients. In an attempt to overcome this difficulty, thrombin times with and without toluidine blue were used to indicate heparin activity. In this reaction the clotting-time of the test plasma on the addition of a solution of thrombin of suitable strength is compared with that of a normal plasma tested at the same time. The presence of heparin delays the reaction and prolongs the thrombin clotting-time. The addition of toluidine blue to heparinized

plasma corrects the thrombin time and confirms the presence of heparin. These studies were performed on seven cases, and the results are summarized in Table V.

Unneutralized heparin was present after protamine in one or more specimens in six of the seven cases. In Case 1 the prolonged thrombin times after perfusion were not corrected by toluidine blue, and it seems possible that this case had developed an antithrombin other than heparin. Insufficient plasma was available to pursue this point further. In Case 3 there was possibly a trace of heparin activity immediately after perfusion, but by the end of the operation there was much more. Since no further heparin had been given this would seem to indicate an escape of heparin from protamine control. Heparin activity was still present in Case 2 on the first post-operative day some 16 hours after perfusion. Possibly the detoxication of heparin was delayed by congestion of the liver.

The coagulation studies are summarized in Table VI. The specimens of plasma are the same as those in Table V. The presence of heparin in many samples renders interpretation difficult, but nevertheless some useful information was gained. Where heparin is present the figures given are the minimum values for the coagulation factors.

The one-stage prothrombin times showed little change throughout the operations apart from the post-operative specimen of Case 3, where the prolonged time was probably due to heparin. There was thus no gross change in factor V or factor VII activity.

The prothrombin estimation by the two-stage method is more sensitive to traces of heparin, but there was a definite decrease in prothrombin activity in Cases 1 and 4 on the first post-operative day at a time when no heparin activity could be detected.

The other four cases examined showed no gross fall in prothrombin activity, but the presence of heparin in many samples rendered exact measurement impossible.

TABLE V.—Heparin Activity as Shown by Thrombin Times (Seconds) of Seven Patients After Extracorporeal Circulation

Case	Sample Tested	Pre-op.	Pre-perf.	Post-perf.	Post-op.	First Day
1	Normal plasma	21	23	23	23	30
	Patient's	23	22	38	36	30
	Patient + toluidine blue*	—	—	37	34	—
	Conclusion	N.	N.	A.	A.	N.
2	Normal plasma	45	45	45	45	32
	Patient's	50	48	70	65	65
	Patient + toluidine blue	—	—	52	50	40
	Conclusion	N.	N.	H.	H.	H.
3	Normal plasma	35	35	35	15	42
	Patient's	35	35	40	120+	47
	Patient + toluidine blue	—	—	—	15	—
	Conclusion	N.	N.	H.P.	H.	H.P.
4	Normal plasma	52	52	52	—	35
	Patient's	50	50	62	—	34
	Patient + toluidine blue	—	—	51	—	—
	Conclusion	N.	N.	H.	—	N.
5	Normal plasma	50	50	50	—	55
	Patient's	52	50	100	—	54
	Patient + toluidine blue	—	—	64	—	—
	Conclusion	N.	N.	H.	—	N.
8	Normal plasma	43	43	43	43	65
	Patient's	43	40	300+	200+	65
	Patient + toluidine blue	—	—	75	80	—
	Conclusion	N.	N.	H.	H.	N.
11	Normal plasma	30	30	30	30	30
	Patient's	29	29	36	30	30
	Patient + toluidine blue	—	—	30	—	—
	Conclusion	N.	N.	H.	N.	N.

N.=Normal. A.=Antithrombin. H.=Heparin. H.P.=Heparin possible.

* The prolonged thrombin time after perfusion in Case 1 was not readily corrected by toluidine blue (see text).

TABLE VI.—Coagulation Factors of Seven Patients After Extracorporeal Circulation

Case	Test Performed	Pre-op.	Pre-perf.	Post-perf.	Post-op.	First Day
1	Heparin activity	Nil	Nil	Anti-thrombin	Anti-thrombin	Nil
	One-stage prothrombin (secs.): Patient	10	11	14	14	13
	Control	11	11	11	11	11
	Two-stage prothrombin (%)	115	66	56	56	35
	A.H.G. assay (%)	140	180	100	70	76
	S.T.G.T. (secs.)	12	13	12	13	15
2	Heparin activity	Nil	Nil	Present	Present	Present
	One-stage prothrombin (secs.): Patient	13	13	15	14	15
	Control	13	13	13	13	13
	Two-stage prothrombin (%)	106	94	104	78	70
	A.H.G. assay (%)	120	160	200+	190	200+
	S.T.G.T. (secs.)	12	13	16	15	15
3	Heparin activity	Nil	Nil	Possible trace	Present	Possible trace
	One-stage prothrombin (secs.): Patient	11	12	14	25	13
	Control	11	11	11	11	11
	Two-stage prothrombin (%)	73	69	69	—	83
	A.H.G. assay (%)	160	130	200+	—	200+
	S.T.G.T. (secs.)	13	11	13	—	—
4	Heparin activity	Nil	Nil	Present	—	Nil
	One-stage prothrombin (secs.): Patient	11	12	13	—	14
	Control	10	10	10	—	12
	Two-stage prothrombin (%)	73	78	44	—	50
	A.H.G. assay (%)	100	110	70	—	37
	S.T.G.T. (secs.)	13	15	14	—	12
5	Heparin activity	Nil	Nil	Present	—	Nil
	One-stage prothrombin (secs.): Patient	11	14	14	—	13
	Control	10	12	12	—	12
	Two-stage prothrombin (%)	80	83	63	—	81
	A.H.G. assay (%)	120	120	200+	—	200+
	S.T.G.T. (secs.)	12	13	15	—	12
8	Heparin activity	Nil	Nil	Present	Present	Nil
	One-stage prothrombin (secs.): Patient	12	12	15	14	12
	Control	12	12	12	12	12
	Plasma T.G.T. (secs.)	12	12	12	12	12
	S.T.G.T. (secs.)	11	11	19	12	13
	Heparin activity	Nil	Nil	Present	Nil	Nil
11	One-stage prothrombin (secs.): Patient	16	16	18	17	16
	Control	15	15	15	15	15
	Two-stage prothrombin (%)	91	91	68	75	87
	A.H.G. assay (%)	160	160	100	100	130
	S.T.G.T. (secs.)	—	—	—	—	—

Notes.—(1) The presence of heparin activity in any sample has been inferred from Table V. and, where present, the figures represent the minimum value for the coagulation factors.

(2) "S.T.G.T." and "plasma T.G.T." mean serum and adsorbed plasma thromboplastin generation tests. The figures indicate the substrate clotting-times in seconds after sampling the incubation mixture at five minutes.

Antihæmophilic globulin assays appeared to be less affected by traces of heparin, possibly owing to the high dilutions of plasma used. Cases 1 and 4 showed decreased A.H.G. levels on the first post-operative day, when no heparin was detected. Unexpectedly three cases showed increased A.H.G. activity following perfusion, persisting for at least 24 hours. There was no change in A.H.G. activity in Case 11, and, although assays were not performed on Case 8, the plasma thromboplastin generation test showed no changes.

The serum thromboplastin generation tests for Christmas factor activity showed little significant alteration. There was slight prolongation of the times in the post-perfusion specimens of Cases 2 and 8, but both these specimens showed heparin activity, rendering interpretation difficult.

Discussion

Reports of blood-coagulation disorders after the use of an extracorporeal circulation are numerous and sometimes conflicting. The most frequent and consistently

observed changes are thrombocytopenia, fibrinogenopenia, and increased fibrinolysis (Osborn *et al.*, 1955; Kay *et al.*, 1956; Effler *et al.*, 1956; Levowitz *et al.*, 1956; Cooley *et al.*, 1957; DeWall *et al.*, 1957, 1959; Brown and Smith, 1958; von Kaulla and Swan, 1958; Smith *et al.*, 1959; Gravel *et al.*, 1959; Rothnie and Kinmonth, 1960a). Activation of coagulation with consumption of coagulation factors has been postulated by Brown and Smith (1958), and a decrease of factor V and A.H.G. levels was later reported by these authors, using "edglugate-Mg" as anticoagulant in donor blood (Smith *et al.*, 1959). On the other hand, DeWall *et al.* (1956) found in a series of patients with acyanotic heart disease and impaired coagulation mechanism that the latter often improved in the immediate post-operative period. The development of a circulating anticoagulant acting against thrombin has been reported by von Kaulla and Swan (1958), and excess of unneutralized heparin following protamine by titration is thought to be of importance by Peden and McFarland (1959) and Rothnie and Kinmonth (1960a).

In 1954 Clowes *et al.* reported a series of operations on 34 dogs in which post-operative bleeding occurred in 14 and disorders of fibrin formation in a further six, but later reports have revealed a much lower incidence of actual bleeding despite the laboratory changes which may occur. Osborn *et al.* (1955) reported that after the elimination of turbulence, foaming, and jets from the extracorporeal circuit the degree of fibrinolysis, fibrinogenopenia, and thrombocytopenia decreased; and among the last 18 dogs perfused only two cases of bleeding occurred, both of which were attributed to a serious mistake in perfusion technique. This group later reported the results of over 150 perfusions in dogs (Osborn *et al.*, 1956). Of the last 15, two died from bleeding; one had severe thrombocytopenia and the other received inadequate protamine. Kay *et al.* (1956) reported only one case with severe bleeding after 44 minutes' perfusion, the cause of which is not stated, and Burchell (1957) found that excessive haemorrhage was rare. Cooley *et al.* (1957) reported two cases with uncontrollable bleeding of unknown cause in a series of 98, but these were early cases. Smith and Brown (1959) have reported one case of bleeding associated with fibrinolysis after 150 minutes' perfusion.

The series of cases reported here is too small to allow statistical analysis of the results, but is useful in emphasizing some of the changes which do occur. A reduction in platelets was almost constant, and this finding is in agreement with most other reports. DeWall *et al.* (1957) found that the initial fall in platelets was followed by a rapid rise, but in a later report (DeWall *et al.*, 1959) these workers found that the thrombocytopenia was maintained on the first post-operative day, a finding in keeping with those reported here. The factors which may lead to a thrombocytopenia are numerous. Apart from the obvious trauma and numerous foreign surfaces to which the blood is exposed, both heparin (Scalabrino *et al.*, 1954) and protamine (Jaques, 1949) may lower the platelet count; a similar finding has been noted after large transfusions (Bell, 1953). It is difficult, therefore, to single out any one factor, and in this series no correlation was found between platelet counts and perfusion times and rates.

Changes in the white cells have been noted by Melrose *et al.* (1953) and DeWall *et al.* (1957). These authors describe a fall in total white-cell counts on perfusion

and a rise soon after. Gravel *et al.* (1959) also found that the white cells fell after perfusion and that a white deposit formed on the walls of the oxygenator which contained fibrin, white cells, and platelets. Kay *et al.* (1956) reported no constant change in the white cells. In the series reported here the neutrophils had risen at the end of perfusion but fell in the next few hours. The removal, *in vivo*, of damaged cells from the circulation might account for the fall in number of circulating neutrophils, and also for the loss of lymphocytes and eosinophils. On the other hand, endocrine response to stress might have played a part in altering the white-cell count. Hills *et al.* (1948) have reported neutrophil leucocytosis, lymphopenia, and eosinopenia after administration of A.C.T.H.

The decreased fibrinolysis on the first post-operative day has not been previously reported. von Kaulla (1958) has reported a refractory period after pyrogen-induced fibrinolysis, during which euglobulin lysis times were prolonged; this period sometimes lasted for 24 hours. The decreased fibrinolysis possibly means that the enzymes or activators have been used up, in which case increased fibrinolysis might have been present earlier in all the cases, though not always at the exact times of sampling. It is not necessary, however, to assume increased fibrinolysis to explain this phenomenon, which could also be due to failure of normal replacement of fibrinolytic enzymes or to the presence of inhibitor in the euglobulin fraction. Plasma fibrinogen was not estimated at this time, but it is unlikely that altered concentrations of this substance would so consistently affect euglobulin lysis. Kowalski *et al.* (1959) have shown that increasing the amount of fibrinogen in the euglobulin fraction does not produce consistent changes in the lysis times. It must be admitted that the exact significance of the finding is not known; nor is it yet known if this is a usual finding after surgical operations without an extracorporeal circulation.

The changes in the coagulation factors here reported are variable. The one-stage prothrombin times were little affected, which confirms the finding of Effler *et al.* (1956). The two-stage prothrombin activities and A.H.G. levels seemed unrelated to euglobulin lysis times or length and rate of perfusion, but the decrease of these factors found in two cases is to be expected if activation of coagulation had occurred either after contact of the blood with foreign surfaces or the release of thromboplastic substances from damaged cells. Unfortunately plasma haemoglobin values as an index of trauma are not available for these particular cases. The increased A.H.G. levels found in three cases were unexpected, although, as mentioned previously, enhanced clotting mechanism following perfusion has been reported (DeWall *et al.*, 1956). The increased A.H.G. levels and decreased fibrinolysis seen in some cases on the first post-operative day indicate that, in some respects at least, the blood may have an increased ability to clot at this time. Post-operative venous thromboses have not, however, been a notable feature of these cases.

The presence of unneutralized heparin in post-perfusion samples after the use of protamine is a potential source of troublesome bleeding. Bleeding has not been encountered here in the last 50 cases treated by February, 1960, but the possibility has led others to use the thrombin time to assess heparin activity and to the use of hexadimethrine bromide ("polybrene") to neutralize its activity (Rothnie and Kinmonth, 1960b).

Summary and Conclusions

A small series of patients undergoing open cardiac surgery utilizing an extracorporeal circulation was investigated to demonstrate the effect of perfusion on certain cellular components and coagulation factors of the blood.

Thrombocytopenia occurred in 12 of the 13 cases and persisted for at least 24 hours. A neutrophil leucocytosis occurred during perfusion, but the count tended to fall to previous levels by the end of the operation. There was a lymphopenia and eosinopenia.

A fall in plasma fibrinogen followed perfusion in 10 of the 13 cases, and there was increased fibrinolysis in five. A constant decrease in plasma fibrinolytic activity was present on the day after operation. The possible significance of this unexpected finding is discussed.

The use of the plasma thrombin time to demonstrate residual heparin activity after protamine neutralization is described, and this was present in six of the seven cases investigated. The other case possibly developed a circulating anticoagulant other than heparin. No tendency to bleed developed in these cases, but the investigation of coagulation factors was rendered difficult by the presence of heparin.

Changes in coagulation factors were investigated in seven cases. One-stage prothrombin times (factor V and factor VII) and serum thromboplastin generation tests (Christmas factor) were not significantly affected by perfusion even in the presence of traces of heparin. Prothrombin activity as measured by the two-stage method was more sensitive to heparin but was not grossly altered in four cases. In two other cases there was a decrease in prothrombin activity on the day after operation. Antihaemophilic globulin levels were variable, being decreased after operation in two cases and increased in three.

No correlation was found between any of the haematological changes and the duration and rate of perfusion. Excess bleeding or purpuric manifestations were not encountered in any patient.

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MUMPS EPIDIDYMO-ORCHITIS AND ITS TREATMENT WITH CORTISONE

REPORT OF A CONTROLLED TRIAL

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Epididymo-orchitis occurs not uncommonly in infections with the mumps virus. Werner (1950a), in a review of the literature, quotes its incidence in mumps as between 11 and 66%, of which 18–30% were bilateral and 48–55% were followed by testicular atrophy. In his own series he noted that 4.9% of all cases of mumps, but 19% of those affected after the age of 13 years, had epididymo-orchitis, the corresponding figures for atrophy being 1.7 and 6.8% of cases of mumps. In an outbreak of mumps under circumstances similar to those forming the material for this study, Ross Russell and Donald (1958) found 48 cases of orchitis among 287 cases of Gurkha recruits with mumps. Candel (1951) noted atrophy in 5.1% and "loss of turgor" in a further 45% of 78 affected testicles seen on discharge from hospital after the attack, but in another group seen by him six years after their acute attack atrophy was present in 55% of 49 originally affected testicles; he suggested that the process of atrophy may continue after the patient becomes clinically symptom-free. Lambert (1951) concluded that testicular atrophy, as determined by quite elaborate measurements and calculations, occurred in 65.8% of cases of mumps orchitis examined by him some time after the attack.

The importance of mumps epididymo-orchitis as a cause of sterility in males is probably not great even in bilaterally affected cases (*Brit. med. J.*, 1959). Benard

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