TABLE 3

HEPARIN LEVELS

I. Donor blood
   A. 2250 U heparin per 500 ml blood — 4.5 U/ml
II. Patient
   A. 2 mgm (200 U) per Kg — 2 U/ml
   B. 3 mgm (300 U) per Kg — 3 U/ml
   C. 4 mgm (400 U) per Kg — 4 U/ml
III. With prolonged bypass, add 1 mgm (100 U) per Kg per hour.

A Survey

Hematologic Complications

of extra-corporeal by-pass

PART II

By HERBERT A. PERKINS, M.D.
Director of Research
Irwin Memorial Blood Bank of the San Francisco Medical Society
Associate Clinical Professor of Medicine
University of California School of Medicine, San Francisco

The patient's platelet count falls to approximately 50% of its initial level within the first five minutes of bypass. A very slow downward drift of the platelet count continues as bypass progresses, the rate of fall depending largely on the amount of additional donor blood administered. Within two hours after completion of a short uncomplicated bypass the count returns toward the normal range. In the more difficult cases the platelet count remains between 60,000 and 100,000 per cu mm for 4-5 days and then returns to normal. Many patients have an abortive rise of the platelet count several hours after surgery, followed by a return to low levels for several days.

Fibrinogen falls moderately during bypass, more so in the longer procedures, but almost never to a level which requires therapy. It rises rapidly in the first few hours after the period of extracorporeal circulation. Factor VIII (antihemophilic globulin) tends to remain normal or even rise in most uncomplicated bypasses. With difficulties in maintaining the circulation, factor VIII will fall. This suggests that the levels of Factor VIII are the net result of its tendency to rise with stress and to be consumed with intravascular coagulation. Factor V and Factor II (prothrombin) remain modestly below the normal range for several days after bypass.

Most of these changes occur to the same degree regardless of the type of pump-oxygenator employed. No differences are apparent between results with heparinized or ACD blood primes, but when total hemodilution is used, there are significantly lower levels of fibrinogen, Factor II and Factor V at the end of bypass. Levels low enough to affect hemostasis were seen only for fibrinogen (with hemodilution). These remained at a significantly low level for only an hour or two (15), and did not require specific replacement therapy.

HEPARIN LEVELS (*Table 3*)

The concentration of heparin in a unit of donor blood has been standardized by the Division of Biologics Standards of the National Institutes of Health, resulting in a heparin level of approximately 4.5 U per ml of whole blood. Doses of heparin administered to the patient generally result in a somewhat lower level. Traditionally these doses have been expressed in mg/Kg. Since heparin is biologically standardized, the dose is incorrectly expressed in mg. When the literature specifies 1 mg of heparin, it really means 100 U. Generally speaking, a dose of 300 U/Kg will result in a blood level of approximately 3 U/ml.

Too little heparin can obviously result in the dangers of intravascular

TABLE 4

PROTAMINE TITRATION
(Rough Technic)

1. Stock protamine = 1% = 10 mgm per ml = 10,000 mcg/ml
2. One drop in 5 ml saline — 5 mcg per drop
3. Tubes with 0, 1, 2, 4, 8 drops provide 0, 5, 10, 20, 40 mcg/ml blood
4. Add 1 ml blood to each and mix
5. Note which tubes have clotted at 15 minutes
6. End point is clotted tube with smallest amount of protamine
7. Dose to patient = mcg in this tube x 100 x patient weight in Kg

coagulation. The original tendency of surgeons to minimize heparin doses in the hopes of decreasing blood loss was obviously incorrect, and numerous teams have noted better hemostasis at higher heparin levels. Over the years we have had a series of experiences which dramatically emphasized the dangers of inadequate heparin. In an early operation in which an aortic bypass was carried out without an oxygenator, it was felt that the minimal heparin dose of 100 U/Kg would be adequate. The procedure was uneventful, but the bypass tubing was covered with a thick layer of fibrin.

At another hospital, a screen oxygenator annoyed the surgeons because of plugging of the holes through which blood was supposed to drop onto the screens. When it was suggested that the heparin dose be raised from 200 U/Kg to 300 U/Kg, plugging of the holes no longer occurred.

This same group met further problems in their initial experiments in the dog laboratory with total hemodilution using a bubble oxygenator. The circuit clotted solid. When it was suggested that the heparin dose be raised from 300 U/Kg to 400 U/Kg, this no longer occurred. The surgeons were unaware of *the well-established facts that dilution of blood (within limits) accelerates coagulation (16) as well as fibrinolysis (17).*

In short, it has been confirmed that blood loss will be less when the heparin dose is raised to adequate levels. It may well be that we are still using insufficient heparin. Larger doses might prevent the usual fall in fibrinogen which accompanies most heart-lung bypasses. There may be no such thing as too much heparin; there is definitely such a thing as too little heparin. Long bypasses are inceasingly common and raise the risk that heparin levels may fall to an unsafe point. Additional heparin must be added to the circuit at intervals to prevent this. We generally add 100 U//Kg per hour.

HEPARIN NEUTRALIZATION

The need to neutralize heparin once the bypass is over and the cannulae have been removed is generally accepted. Any heart-lung bypass is followed by at least a short period of abnormal bleeding due to incisions in high pressure areas of the circulation and changes in the platelets and blood clotting factors. Heparin will exaggerate this. Neutralization may be carried out with either Polybrene R or protamine; the former, however, is no longer available. These heparin neutralizers may have serious side effects if given too rapidly. Apnea, bradycardia and hypotension are well-documented (18). Aggregation of red cells and disappearance of platelets may occur.

In gross excess, these agents are weak anticoagulants and can combine with and remove Factor VIII (19). The usual neutralizing dose of protamine is between 1.2 and 2 times the original dose of heparin (in mgm) given to the patient. This amount, administered slowly, should have no side effects. If abnormal bleeding continues, and the clotting time remains prolonged, a further half dose may be given.

In prolonged bypasses, heparin saturates the tissues and may not be entirely neutralized by the initial dose of protamine. Diffusion of heparin back into circulation may be one explanation for the phenomenon of heparin rebound (20). Prolonged bypasses may thus be followed by a routine of administering half the original neutralizing dose an hour later. When in doubt as to the need for further protamine, it is safest to confirm the need *in vitro* by protamine titration (21). This may be done rather simply but adequately by the method outlined in *Table 4*.

The thrombin time has been widely used to evaluate the presence of circulating heparin. This test is far more sensitive to heparin than the whole blood clotting time technic described above, but is technically more difficult and has the added disadvantage that it may be prolonged for reasons unconnected with heparin. If intravascular coagulation and fibrinolysis have occurred, fibrin breakdown products will prolong the thrombin time. The problems created by the use of protamine have lead some teams to suggest that neturalization of heparin may be omitted following uncomplicated short bypasses.

CAUSE OF ABNORMAL BLEEDING (*Table 5*)

If abnormal bleeding results during surgery because of a pre-existing hemostatic defect, the nature of the underlying defect will be occurred by changes due to the procedure itself and there will be no time for sophisti-

(Turn to Page 20)

TABLE 5

CAUSES OF ABNORMAL BLEEDING

1. Pre-existing defects
2. Intravascular coagulation
3. Fibrinolysis
4. Transfusion therapy
5. Dirt and endotoxin
6. Protein denaturation

cated tests of hemostasis. It is thus essential to detect and diagnose hemostatic defects before surgery is begun. Pre-existing defects can be ruled out if a careful history reveals no abnormal bleeding despite adequate provocation; i.e. prior trauma or surgery. If doubt exists; the tests listed in *Table 6* are sufficient to rule out significant defects.

Children with severe degrees of polycythemia secondary to cyanotic congenital heart disease present a special problem. Falsely abnormal laboratory results are frequently reported because of failure to reduce the volume of anti-coagulant in proportion to the plasma fraction. Moreover, it is difficult to obtain the viscous blood rapidly enough to prevent incipient coagulation in the sample with loss of platelets and clotting factors *in vitro*.

On the other hand, there is no question that these polycythemic children may bleed abnormally at surgery. An unstable clot can result from a disproportion between a normal concentration of fibrinogen and the very large red cells mass which must be held together by the fibrin network. This reflected *in vitro* by excessive fall-out of red cells from the clot.

Hemostasis may also be impaired because of low grade intravascular coagulation secondary to sluggish flow of the very thick blood. In extreme cases a moderate preoperative reduction of the hematocrit may be advisable and early heparinization has been suggested (22). These prophylactic approaches have not yet been adequately investigated in terms of safety and effectiveness.

TABLE 6

PRE-EXISTING HEMOSTATIC DEFECTS

A. Adequate history may avoid need for tests.
B. Quick prothrombin time
1. Bleeding time, preferably by the technic of Ivy
2. Platelet count
3. Quick prothrombin time
4. Partial thromboplastin time
5. Clot observation for
   a. Retraction
   b. Red cell fall-out (relatively low fibrinogen)
   c. Lysis

REFERENCES

5. Perkins, H. A.: unpublished studies.
6. Perkins, H. A., C. Thacher and M. R. Rolfs: Measurement of Calcium Ion Levels During Massive Transfusion of Citrated Blood. Proc. Internat. Transfusion Soc. 10: 1145, 1965.
7. Long, D. M., Jr., L. Sanchez, R. L. Varco and C. W. Lillihei: The Use of Low Molecular Weight Dextran and Serum Albumin as Plasma Expanders in Extracorporeal Circulation Surgery 50: 12, 1961.
8. Ewald, R. A., J. W. Eichelberger, Jr., A. A. Young, H. J. Weiss and W. H. Crosby: The Effect of Dextran on Platelet Factor 3 Activity: In Vitro and In Vivo Studies. Transfusion 5: 109, 1965.
9. Perkins, H. A., M. R. Rolfs, A. Mc Bride and B. Roe: Low Molecular Weight Dextran in Open Heart Surgery. Effect on Coagulation Factors and on Red Cell Antibody Activity. Transfusion 4. 10, 1964.
10. Breckenridge, I. M. and W. F. Walker: Blood Loss in Open Heart Surgery with Low Molecular Weight Dextran. Lancet 1: 1190, 1963.
11. Hellstrom, G. and V. O. Bjork: Hemodilution with Rheomacrodex during Total Body Perfusion. J. Thoracic Cardiovasc. Surg. 45: 395, 1963.
12. Neville, W. E., L. P. Faber and H. Peacock: Total Prime of the Disk Oxygenator with Ringer's and Ringer's Lactate Solution for Cardiopulmonary Bypass. Clinical and Experimental Observations. Dis. Chest 45: 320, 1964.
13. Perkins, H. A., M. R. Rolfs and D. J. Acra: Studies on Bank Blood Collected and Stored under Various Conditions with Particular Reference to Its Use in Open Heart Surgery. Transfusion 1: 151, 1961.
14. Schmidt, P. L., J. C. Peden, Jr, G. Brecher and A. Baranovsky: Thrombocytopenia and Bleeding Tendency after Extracorporeal Circulation. New Eng. J. Med. 265: 1181, 1961.

INTRAVASCULAR COAGULATION

A major cause of abnormal bleeding due to heart-lung bypass is intravascular coagulation, which has already been mentioned above in the section on heparin. Numerous mechanisms for induction of this dangerous condition exist (*Table 7*), and it probably occurs to some extent in all bypasses. The tendency toward clotting in the circulation is increased whenever stagnation occurs.

(To Be Continued)

TABLE 7

CAUSES OF INTRAVASCULAR COAGULATION

A. Exposure of blood to foreign surfaces
B. Liberation of partial thromboplastins from destroyed red blood cells and platelets
C. Oozing of tissue juices (thromboplastin) from injured surfaces
D. Damage to endothelium of blood vessels
E. Bacterial endotoxin
F. Antigen-antibody reactions
G. Stagnant circulation
1. Poor perfusion
2. Decreased blood volume
H. Inadequate heparin level to compensate for above