THE FEASIBILITY AND PHYSIOLOGICAL ASPECTS OF ANESTHESIA AND

SURGERY WITHOUT HOMOLOGOUS BLOOD TRANSFUSIONS

PROEFSCHRIFT

TER VERKRIJGING VAN DE GRAAD VAN DOCTOR IN DE

GENEESKUNDE

AAN DE ERASMUS UNIVERSITEIT ROTTERDAM

OP GEZAG VAN DE RECTOR MAGNIFICUS

PROF. DR. J. SPERNA WEILAND

EN VOLGENS BESLUIT VAN HET COLLEGE VAN DEKANEN.

DE OPENBARE VERDEDIGING ZAL PLAATSVINDEN OP

WOENSDAG 1 JUNI 1983 DES NAMIDDAGS

TE 2.00 UUR

DOOR

RONNY LAPIN

GEBOREN TE TEL AVIV

This manuscript is dedicated
with love to my son Ari.

LIST OF CONTENTS

'The credit belongs to the man who is actually
in the arena whose face is marred by dust and
sweat and blood; who at best knows in the end
the triumph of high achievements and who at
worst if he fails at least fails while daring
greatly so that his place shall never be with
those cold and timid souls who know neither
victory not defeat.'

Franklin T Roosevelt

CHAPTER I

INTRODUCTION

The modern practice of medicine has an ever-increasing dependency on the blood bank industry. Indeed, on many occasions there is an unwarranted and inappropriate use of hemotherapy.

The first recorded blood transfusion was given to Pope Innocent VIII in 1492 (Narengo-Rowe, 1982). This treatment was unsuccessful, and the patient and all three blood donors died as a result of the experiment. Since then physicians have been mesmerized by the 'omnipotent' powers of extraneous blood in reversing disease processes, regardless of the inherent complications or the logical indications for such blood transfusions.

It has been estimated that 12 million units of blood are transfused yearly into patients in the United States. This blood comes primarily from volunteer sources, but paid donors must necessarily be used, in order to make up for shortages created by the ever increasing demand. In addition, the cost of whole blood has risen steadily to $100.00 per unit in some hospitals and frozen blood is double this price. On average 2.5 units of blood are used for each transfusion and retrospective data analyses of the need for individual blood transfusions have uniformly demonstrated that at least half of all blood transfusions were unnecessary.

The risks of using homologous blood include isosensitization, disseminated intravascular coagulopathy, febrile reactions, bacterial contamimation, thrombophlebitis, hepatitis, cytomegalic viruses infection, syphilis, herpes, malaria, trypanosomiasis, thrombocytopenia, and reduced factor-VIII mediated coagulopathy. Cardiac arrhythmias may occur as a result of vascular overload and hemosiderosis.

Blood, mismatched as a result of technical errors has also sometimes contributed to catastrophies. The risk of hepatitis is 20-46% with paid donors,

and ranges from 10-15% when volunteers are used for the provision of donor blood. Since only one-third of the patients become clinically jaundiced, it is difficult to determine the total incidence without performing liver enzymes tests and antigen screening studies in all cases. The exact number of deaths directly related to the transfusion of blood is also difficult to determine due to various factors (including the failure of many hospitals to report such occurrences). Of the deaths which have been attributed to blood transfusion, 60% were related to mismatched blood and 30% resulted from serum hepatitis (Myhre, 1980).

A number of methods can be employed in order to avoid the use of blood transfusions. For additional information the reader is referred to Fig. 1 in which the subject is dealt with schematically.

Surgical techniques may be improved, in order to avoid blood loss, by employing hypotension, hypothermia, autotransfusion, intravenous iron therapy, Folic Acid, and intravenous hyperalimentation to increase the rate of natural hemoglobin production. Reassessment of the concept of the 'need' for a hemoglobin of 10 gm%, exploring the full potential of perfluorochemicals, and the use of erythopoietin will greatly reduce the costs, risks, and shortages which are associated with autologous blood transfusions.

Grant (1921) reported the first peroperative autologous blood transfusion. Milles (1963) documented a similar procedure and Cowell (1974) presented a report on a series of pediatric orthopaedic patients who were treated using this method of autologous transfusion. The safety of preoperative blood collection for subsequent retransfusion into patients with coronary insufficiency was demonstrated by Cove (1976) and Ebert (1941) showed that plasma volume will increase over 72 hours to compensate for the loss of red blood cells. Finch (1950) showed that the limiting factor to effective hematopoesis after blood loss is the depletion of iron-stores. Total dose infusion of intravenous Iron was shown to replace these stores quite rapidly.

Mallory (1976) and Eckhardt (1978) reported two series of patients undergoing hip replacement utilizing preoperative blood harvesting. The average blood

donation was 2.6 units per patient. Mallory stored liquid blood for only 8 days before retransfusion, while Eckhardt used 4 day intervals between donation and infusion. Blood in the former study was citrated and stored at 4°C. Frozen red cells were drawn at 6 day intervals and stored with glyceryl at -87°. Fifty-five percent of the patients in both groups required no additional blood following surgery. This method does not require sophisticated handling or new anesthetic techniques, though the cost involved in freezing red blood cells is not insignificant. Some reports have shown a decrease in the rate of hepatitis transmission in patients receiving homologous and autologous frozen blood.

When blood loss during surgical procedures is estimated preoperatively to be greater than 500 cc's, acute isovolemic hemodilution may be performed in those patients not suffering from coronary artery disease or congestive heart failure. This technique was originally planned to be used to conform with the religious objections of Jehovah's Witnesses. These patients will not accept any type of blood storage or homologous blood transfusion. Witnesses will also not accept this technique of hemodilution if blood is removed from their own circulation and storage takes place before reinfusion. This technique of isovolemic hemodilution can conserve 2-3 units of whole blood. It is accomplished by removing as much as 50% of the patient's red blood cells prior to actual surgery, and then replacing the volume by using crystalloid solutions in a ratio of 3:1. This type of dilution will reduce the patient's hematocrit under control conditions, thus minimizing the operative red cell loss by nearly 50%.

The first intraoperative autotransfusion was reported by Blundell (1818) and the technique was later employed in intracranial surgery by Cushing (1925). Carbon monoxide intoxication has been treated by Highmore (1874) using these methods. The practical application of intraoperative hemodilution was shown by Laks (1974). In a series of total hip replacement patients, he demonstrated the compensatory ability of the body to overcome decreased tissue oxygenation through increased cardiac output. No changes were reported in the lactate-pyruvate ratio, muscle surface pH or the patient's arteriovenous oxygen difference.

Retransfusion of the patient's own blood reduces the hazard of serum hepatitis, as well as the risk of mismatched blood (all of which can occur with homologous transfusions). With further modification, such as the elimination of autologous blood storage, this technique is accepted by the Jehovah's Witness patient.

Using the 'cell-saver' apparatus (manufactured by the Haemonetics Corporation), Flynn (1981) reported 55% harvesting of the red blood cells which would have normally been 'lost' during surgery. He studied 125 patients undergoing orthopaedic procedures (mainly spinal fusions). Turner (1968) also salvaged as much as 61% of the red blood cells in his series. Bonnett et al. (1981) reported similar results.

The cell salvage rate can be increased to as much as 90% by keeping the tissues moist, wringing-out sponges, and the meticulous use of the suction apparatus. When continuous blood loss occurs in the recovery room (or in the intensive care unit) from surgical drains, the cell-saver can be used in the continuing effort to recover RBC's. We have had no complications from this technique. The new computerized-model cell-saver can easily be operated by the anesthesiologist, thus eliminating the need for a technician and thereby reducing the cost.

Hypotension may be employed to reduce intraoperative blood loss and was first reported by Gardner (1946), using arteriotomy and subsequent reinfusion. Hypotension may also be induced by high spinal anesthesia and ganglionic blocks.

Anesthesia employing induced hypotension can be regarded as a method in which a significant portion of the circulating blood volume is pooled, only to be reintroduced to become a significant part of the effective circulatory volume at a later date. Complications of this procedure (as reported by Little (1955) include cerebrovascular accidents and anoxia. There were 113 deaths in 12,264 patients treated with hypotensive anesthesia. By excluding patients with renal disease, and also those patients on antihypertensive medications, Charnley (1974) showed that hypotensive anesthesia decreased blood loss during surgery, decreased

operative time and reduces the number of blood transfusions needed.

By maintaining intraoperative systolic blood pressures between 60 and 75 mm Hg, Davis et al. (1979) reported a reduction of blood replacement by 45% during hip surgery; his patients received Halothane and Pentolinium anesthesia. Mallory (1976) reported a 50% decrease in post-operative homologous transfusions, and 25% reduction in total operative time. Thompson et al. (1978), in a series of patients undergoing hip surgery, demonstrated a 55% decrease in estimated blood loss with Halothane-induced hypotension, and a 65% reduction when hypotension was obtained using nitroprusside. All three investigators saw no increase in the incidence of postoperative hemorrhage, and no hepatic, renal, or myocardial complications were observed. We have obtained similar results with our patients.

A skilled and informed anesthesiologist can easily apply these hypotensive techniques and can also induce hypothermia in order to reduce intraoperative blood loss.

Little, if any, attention has been paid to the improvement of surgical techniques and the refinement of surgical instruments in the medical literature in recent years. The electrocautery and the carbon dioxide laser device have dramatically reduced blood loss without compromising wound healing.

In the present series of 5000 Jehovah's Witness patients, the incidence of wound infections, delayed wound healing, wound dehiscence or 'burst abdomen' was no different to the incidence reported in patients who underwent conventional surgery. In this series blood loss was reduced to 70% of that occurring in a comparable series.

The craftsmanship of the surgeon, and the refinement of his instruments, is as important in reducing blood loss as any other factor. The blind reliance on the blood bank to compensate for the loss of blood resulting from technical laxity during surgery must be changed.

Several years ago, the idea that some man-made fluid could take over the oxygen-carrying capacity of human blood was a dream. Now it is a reality with Fluosol-DA 20%. This milky-white fluid is the by-product of the petroleum

industry. It is closely related to Teflon and holds the promise of making important contributions in patient therapy and research.

Fluosol-DA 20% belongs to a family of synthetic organic chemicals (called perfluorocarbons) in which oxygen solubility is very high. They were developed during World War II as an off-shoot of the 'Manhatten Project'. Fluosol-DA 20% is an emulsion of perfluorodecalin and perfluorotripropelennamine, as well as hydroxyethyl starch. It contains a mixture of electrolytes to maintain osmotic pressure, and contains no clotting or immunological factor.

To date, Fluosol emulsion has been injected into 490 patients in Japan without any serious side-effects. Fluosol has a life span in the circulation of only 72 hours. It is, however, being constantly improved by the researchers of the Green Cross Corporation under the direction of Doctor Naito. It is hoped that the new generations of perfluorocarbons (called Fluosol-DA 35-2) will not have to be stored in a frozen state (as is necessary for Fluosol-DA 20%), and can be used effectively in patients without the need for the high tension oxygen mask. The present generation of perfluorocarbons have proved themselves to be relatively atoxic in animal experimentation, though a certain amount of culmulation is seen in the reticuloendothelial system. In clinical work, this has not limited their usefulness, and potential allergic reactions have been avoided by the concomitant use of corticosteroids.

The potential capabilities of such oxygen-carrying fluids are only limited by man's own imagination. Their advantages are long-shelf life, no hepatitis, the elimination of typing and cross-matching blood, and Fluosol's relative low cost. It can be used in the Third World countries where modern blood banks are still in their infancy.

In the United States, we have the largest series of patients to date who have received Fluosol-DA 20%. This amounts to 17 patients at the moment. We are gratified and impressed by the ability of this product to carry oxygen in those patients who refuse blood transfusions. These Jehovah's Witness patients, some of whom had very low haemoglobin concentrations, received an average dose of 20

ml/kg, and were then able to undergo emergency surgery. There were no intraoperative mortalities and in the most anemic patient Fluosol carried as much as 45% of the consumed oxygen.

Fluosol-DA 20% is an oxygen-carrying fluid which can be extremely helpful when blood is unavailable, or when it cannot be used for various reasons. It has never, however, been the intention that it should completely replace the necessity for the use of blood. It is not metabolized, but rather 'picked up' by the reticuloendothelial system. It is transported to the liver and excreted through the lungs and the skin. We have not encountered any serious complications from its use.

Recent interest in the availability of erythropoietin (which increases the rate of hemoglobin production in clinical situations) has offered another interesting new avenue for decreasing reliance on the blood bank. Perhaps when new data on the use of this substance becomes available, it can be combined with the already-existing methods of reducing blood use.

It is our hope that by combining the features, techniques and the ideas described above, our dependency on the blood bank will be reduced. We will describe all of these techniques in detail in this manuscript. Attempts will be made to demonstrate that the best way to avoid transfusions is to exercise great care in the operating room and that, if transfusions are needed, the best blood one can give a patient is his own.

Proposed Plan for the Reduction of Homologous Transfusion

Techniques to Reduce Blood Loss

1. Refined surgical approach
2. Reduce operative blood loss
3. Modify surgical procedures and strategy
4. Adopt different anesthetic techniques
5. Instrumentation
 a. cautery
 b. laser
6. Hypotension
7. Autotransfusion
8. Hypothermia

Blood Substitutes

1. Perfluorocarbons
2. Volume replacement
 a. Dextran
 b. Gelatine
 c. Starch solution
3. Bone marrow stimulation
 a. Imferon
 b. Folic acid
 c. Anabolic steroids

Fig 1: A schematic overview of a number of methods that can be employed in order to avoid the use of blood transfusions.

First the Nazis went after the Jews but I was not a Jew
so I did not object. Then they went after the Catholics
but I was not a Catholic so I did not object. Then they
went after the Trade-Unionists but I was not a Trade-
Unionist so I did not object. They came after me and
there was no one left to object.

Martin Niemoller,
German Theologian.

.

CHAPTER II

SURGERY WITHOUT BLOOD TRANSFUSION

II- i   The Performance Of Major Surgery In Jehovah's Witnesses.

General Considerations

The performance of major surgery in Jehovah's Witnesses presents the majority of physicians with a moral and ethical dilemma. This is because most doctors see only an occasional member of this religious group during a lifetime of practice. The few physicians who treat these patients on a regular basis are confronted with a great challenge but, at the same time, achieve a great sense of satisfaction after successful completion of therapy.

Since we believe that most physicians are not well acquainted with the moral, legal, and ethical issues involved in the surgical treatment of Jehovah's Witness patients, we present the following combined series, which, to the best of our knowledge, is the largest ever reported in either the U.S.A., or the world literature. It is our hope that this article will not be viewed as a mere collection of numbers and statistics, but rather as a testimony to the fact that major surgery can be carried out successfully on patients who, because of strong religious convictions, refuse to accept transfusions of blood, or blood products.

Clinical Material and Results

From 1973 to 1982, 4,632 patients ranging in age from 1 month to 96 years underwent major surgery without the use of blood or blood products. Twenty two patients died within 4 weeks following surgery from a variety of reasons. This represents a postoperative mortality of 0,48%. Wound infection rate was 5,9%,

Table I: Estimated Blood Loss and Operative Time in Major Surgery - From 1980-1982

Procedure	No. of Cases	Blood loss in cc	Average Operation Time in minutes
Cholecystomy	115	55	20
Common Duct Expr.	11	70	40
Gastrectomy sub total	23	105	45
Gastrectomy total	5	140	65
Vagotomy & pyloroplasty	33	60	30
Total abdominal hysterectomy	85	70	25
Right Colectomy	19	90	45
Left Colectomy	21	130	40
Total Colectomy	8	160	85
Splenectomy (elective)	17	40	28
Splenectomy (emergency)	6	350	40
Gastroesophageal antiflux	16	75	45
Nephrectomy	29	190	60
Total esophagectomy	7	375	90 (2 team approach)
Esophegogastrectomy	9	230	70
Abdominal pereniel resection	67	140	63
Abdominal aneurysm resection (elective)	9	275	80
Modified Radical Mastectomy	45	130	60
pneumonectomy	4	200	75
Lobectomy (lung)	14	250	80
Coronary bypass (1-4 vessels)	109	675	100

and postoperative incisional hernia rate was 3,7%. Four cases of total disruption of the abdominal wall occurred. One patient died from frank hemorrhage. There were two cases of disseminated intravascular coagulation.

These patients were operated upon in two small community hospitals with a total capacity of approximately 300 beds. Three thousand nine hundred and fifty were classfied as general and gynecological, while the remainder were operated upon by specialists in orthopaedics, urology, neurosurgery, cardiovascular or thoracic surgery. The overall average blood loss was 140 cc per case. The types of procedures performed were as follows:

General surgery: Esophagectomy, gastrectomy, cholecystectomy, common duct exploration, biliary diversion procedures, hepatic lobectomy, small and large bowel resection, combined abdominoperineal resection, portosystemic shunts, splenectomy, exploration of abdominal trauma, mastectomy with and without reconstruction, thyroidectomy, herniorrhaphy, antireflux procedures, abdominal aneurysmectomy both elective and emergency, peripheral vascular bypass operations, amputation of the extremities, abdominal wall reconstruction, and reduction and augmentation mammoplasty. The numbers of the different operations together with the estimated blood loss is shown in Table I.

Gynecology: Total abdominal hysterectomy, bilateral salpingo-oophorectomy, cesarean section, vaginal hysterectomy, anterior and posterior repair, and uterine suspension procedures.

Thoracic: Lobectomy, pneumonectomy, pacemaker insertion (either transvernous or transthoracic), pericardectomy, transthoracic repair of hiatus hernia, and esophagectomy.

Neurosurgery: Excision of meningioma and glioma.

Cardiovascular: Coronary artery bypass, repair of ventriculoseptal defect, repair of atrioseptal defect, mitral and aortic valve replacement.

Orthopaedics: Total hip replacement, total knee replacement, cervical fusion, lumbar disc surgery, Harrington rod insertion and spinal fusion for scoliosis, open reduction and internal fixation of fractures in both upper and lower

12

extremities, and pinning of hip fractures. In total 331 procedures were carried out.

Urological: Partial or total nephrectomy, antireflux procedures, nephrolithotomy, ureterolithotomy, pyelolithotomy, transurethral resection of the prostate, open prostatectomy, repair of hypospadias, or Marshall-Marchetti procedure and cystectomy.

Expeditious preoperative workup, prompt surgical intervention in all cases of haemhorrage, meticulous surgical technique, and good surgical assistance were stressed in every case. Blood was not typed or crossmatched, either before or after surgery. Prior to surgery each patient signed an informed surgical consent form, as well as a form releasing the hospital and the physician from responsibility for untoward complications arising from the patient's refusal to accept blood or its derivatives.

Intraoperative autotransfusion, hypotensive and hypothermic anesthesia was used in less than 5% of the cases. Crystalloid solutions, dextran, and hydroxyethylstarch were used for volume replacement. Intravenous Imferon (iron dextran), folic acid, B-12, and Deca-Durabolin (nendralone decanoate) were administered liberally both peroperatively and postoperatvely. The great reduction in blood loss can be primarily attributed to the extensive use of electrocautery in these patients.

Emergency and elective procedures were performed on patients whose hemoglobin levels ranged from 1.6 gm% to 18.0 gm%. One hundred and five patients were operated upon with a preoperative hemoglobin concentration below 5.0 gms% and there was no subsequent mortality in these cases. With 92% follow-up, only 1 death was attributed directly to exsanguination, and only 1 patient had to be returned to the Operating Room for hemostatic control following his initial surgery.

Fluosol-DA 20% was administered to 9 patients, in 6 of whom successful operations were subsequently carried out.

Discussion

The Jehovah's Witness organization was founded in 1881 by Charles Taze Russell in Pittsburgh, Pa. From 1879 until 1930 the group was called the Watchtower and Bible Tract Society. In 1951, under the leadership of Judge Rutherford of Missouri, the society adopted the name of Jehovah's Witnesses. The society is extremely prolific, publishing two bimonthly magazines entitled The Watchtower and Awake. These journals are published in 82 languages.

Most, if not all, of their confrontations with the medical profession have been over their steadfast refusal to accept transfusions of blood or blood products. The reference most frequently quoted by them to substantiate their beliefs is as follows: 'For it is the life of all flesh, the blood of it is for the life thereof. Therefore I said unto the children of Israel, ye shall eat the blood of no manner of flesh for the life of the flesh is the blood thereof. Whoever eateth it shall be cut off' (Leviticus).

Jehovah's Witnesses recognise no difference between the eating of blood and the receiving of it intravenously; thus they vehemently resist transfusions. In their widely quoted publication, 'Blood, Medicine and The Law of God', 'Jehovah's Witnesses' and the 'Question of Blood', they clearly and succinctly make their fundamental beliefs known. They reject not only whole blood but also blood products such as albumin and plasma. They will allow the administration of any blood substitutes such as: glucose, dextran, saline, lactated Ringer's etc. In addition, the society does not approve the use of an individal's own stored or frozen blood. Thus, the surgeon's attempt to draw two units of blood prior to surgery, for the purpose of storage and later transfusion, will usually be rejected by the patient.

Surgical thinking has never been unanimous on the subject of blood trans-fusions. Not only do many now accept that surgery is possible without blood transfusions, but also leaders in many surgical fields are recognizing definite advantages in transfusionless surgery. Cooley (1971) stated: 'We believe that our experience demonstrates the feasibility of open heart surgery in Jehovah's

Witnesses, and moreover, indicates that blood transfusions can, and should be used sparingly to reduce the morbidity and mortality in all patients'.

Roen and Velcek (1972) reported on their observations in urological surgery: 'Our experience with Jehovah's Witnesses requiring operative procedures has demonstrated to us that blood transfusions are not necessarily essential even when the hemoglobin levels are as low as 5.0 gm%, as in one of our cases. The only requirement is a careful and more meticulous operative technique'.

Jehovah's Witnesses believe that physicians should not be expected to perform operations under conditions that they themselves sincerely believe would spell failure. They do not ask the impossible, but evidence is conclusive that they have not always had the benefit of the 'possible'. Some have mistakenly interpreted this stand of Jehovah's Witnesses as one in which an individual is exercising his right to die. There is no such suicidal fanatisism in the thinking of the Jehovah's Witnesses. The very opposite is true; they are determined to exercise every precaution, at whatever cost, in order to obey what they consider God's law in all matters and thereby be assured of life, if not now, then in the future. In patients whom we have treated, we have carefully adhered to the requirements listed in Table II in order to perform surgery and our experience indicates that Jehovah's Witnesses are extremely cooperative and pleasant to work with and that they follow instructions well, as long as they are certain that their religious beliefs will not be compromised.

As far as is known, no Jehovah's Witness has ever filed a lawsuit against an American physician for failing to administer blood. On the contrary, these patients have consistently attempted to resolve any grievances that they might have with the medical profession through their own judicial committee. We firmly believe that a patient, regardless of his religious beliefs, should be entitled to make what he considers the proper decision concerning his medical treatment and that the physician who chooses to treat such a patient is morally bound to adhere to such guidelines regardless of the circumstances.

Understandably, caring for Jehovah's Witnesses might seem to pose a dilemma

TABLE II: Considerations for successfully performing surgery in
Jehovah's Witness Patients.

Absolute respect for the patient's religious rules
Evaluation for the chances of success
   a. Previous experience
   b. Published successes of others
Blood release form signed by both husband and wife
Informed surgical consent
Coagulation screening
Meticulous patient work-up
Competent surgical assistance
Sound surgical planning
Meticulous intra-operative hemostasis
Availability of autotransfusion devices
Availability of Fluosol-DA 20%

for the physician dedicated to preserving life and health by employing all the techniques at his disposal. Editorially prefacing a series of articles about major surgery on Witnesses, Harvey (1980) admitted 'I do find annoying those beliefs that may interfere with my work'. But, he added: 'Perhaps we too easily forget that surgery is a craft dependent upon the personal technique of individuals. Technique can be improved'.

Bolooki (1981) took note of a disturbing report that one of the busiest trauma hospitals in Dade County, Florida, had a 'blanket policy of refusing to treat' Witnesses. He pointed out that 'most surgical procedures in this group of patients are associated with less risk than usual'. He added: 'Although the surgeons may feel that they are deprived of an instrument of modern medicine ... I am convinced that by operating on these patients they will learn a great deal'.

Rather than consider the Witness patient a problem, more and more physicians accept the situation as a medical challenge. In meeting the challenge they have developed a standard of practice for this group of patients that is accepted at numerous medical centers around the country. These physicians are, at the same time, providing care that is best for the patient's total care. As Gardner et al. (1946) observed: 'Who would benefit if the patient's corporal malady is cured but the spiritual life with God, as he sees it, is compromized, which leads to a life that is meaningless and perhaps worse than death itself'.

Witnesses recognize that, medically, their firmly held conviction appears to add a degree of risk and may complicate their care. Accordingly, they generally manifest unusual appreciation for the care they receive. In addition to having the vital elements of deep faith and an intense will to live, they gladly cooperate with physicians and medical staff. Thus, both patient and physician are united in facing this unique challenge.

The trend in medicine appears to be toward treating the 'whole man'. With regard to Jehovah's Witnesses, this involves recognizing that their welfare would not be served by violating their fundamental religious convictions concerning blood.

Since the bulk of the authors experience has been with adult patients, it is difficult to comment on surgery in children, for whom special consideration must obviously be given. However, when faced with surgical procedures in children, where extensive blood loss was anticipated, it was either recommended that surgery should not be performed at that point, or these children were referred to centers where sympathetic physicians were willing to accept such cases.

The majority of articles regarding the treatment of Jehovah's Witnesses without blood transfusion have dealt with cardiovascular surgery. We hope that surgeons who have experience in other specialties and who have been treating Jehovah's Witnesses for some time will publish results of their work in this most controversial area.

We would argee with the statement by Kelly (1967) that 'No doctor can be positive that a person will die if he does not get a transfusion or live if he does. It is perhaps better that the odd person die, rather than that the fundamental right of refusing medical treatment be impaired. Patients have the right to accept or reject a doctors advice according to their desires ....'

The availability of Fluosol-DA 20% which possesses the capability of carrying oxygen has been very encouraging and has made treatment possible in a highly selected group of cases. We hope that when the efficacy of this material is finally proven, much of the resistance against the treatment of Jehovah's Witness patients on the part of the medical profession will subside.

Finally, we wholeheartedly agree with Dunphy (1978) who has said: 'Transfusion certainly makes the surgeon feel better. Perhaps we all have the tendency to transfuse to make ourselves more comfortable ...' When treating a Jehovah's Witness patient, we will do well to consider his point of view.

II-ii   The Surgical Approach to the Jehovah's Witness Patient Bleeding from
        Oesophageal Varices.

The successful surgical management of bleeding esophageal varices in the cirrhotic patient remains, as always, a great dilemma. The questions of when to operate, on whom, what procedure to use or if to operate at all, remains, as they have been in the past, mostly unanswered. These problems become greatly magnified in scope and complexity when the patient in question is also a Jehovah's Witness who steadfastly refuses to accept blood or blood products even at the risk of dying.

Realizing that the best operation for a particular patient is not necessarily the best operation possible, we will attempt in this paper to describe our experience with five cirrhotic Jehovah's Witness patients presenting with bleeding esophageal varices.

Materials and Methods:

Five Jehovah's Witness patients, one male and four females, were treated for active gastrointestinal bleeding which was endoscopically diagnosed as being from esophageal varices. Two patients had previous duodenal ulcer disease and one had ulcerative colitis for which she had a total colectomy and ileostomy performed in the past. One patient had documented Laennec's cirrhosis during a prior operation when a liver biopsy was performed at the time that a mesocaval shunt was attempted but had to be aborted because of technical complications. The other four patients had post-necrotic cirrhosis; two patients were classified as Class A, two as Class B and one as Class C on the Child Scale of Classifications. One patient had thrombocytopenia purpura. The surgical indications for these patients were anemia secondary to poorly controlled variceal bleeding by medical means.
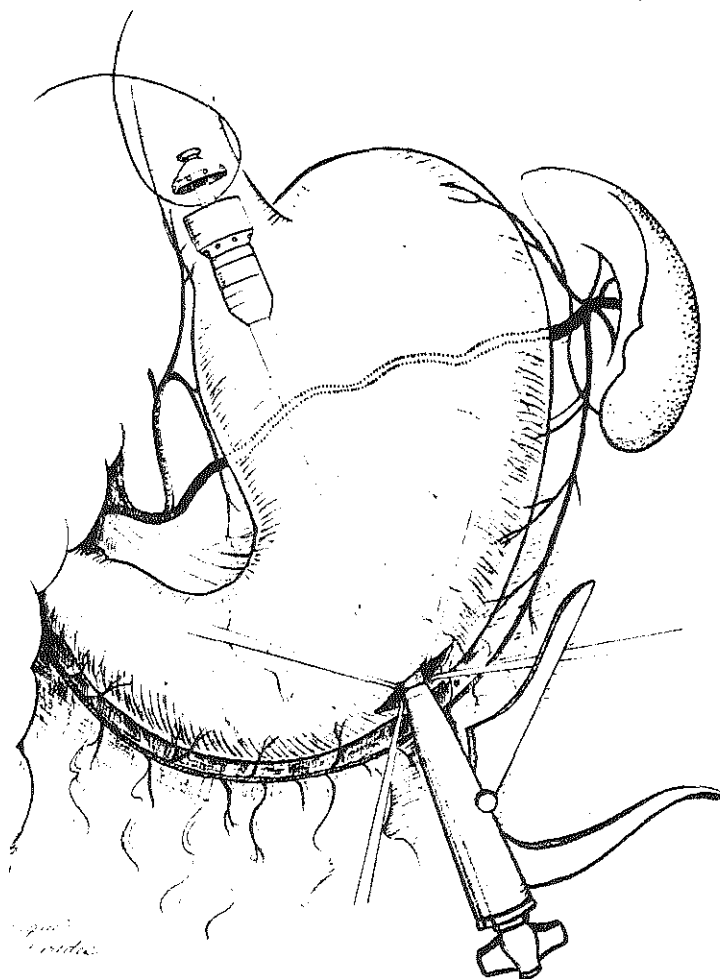
Fig 2:   Showing the EEA stapler in position prior to fixation

20

Operative Techniques

After adequate fluid resuscitation the patients were taken to surgery and given general endotracheal anesthesia. Induction of anesthesia was accompliched with Ketamine and Ativan (Lorazepam) and the patients were carried on Fluothane (Forane) and Pavulon (Pancurodium Bromide). The patients were kept well oxygenated and as light as possible. The abdomen was entered through a generous upper midline incision. Liberal use of the electrocautery was employed in performing the operation and meticulous hemostasis was established throughout the procedure. The left lobe of the liver was retracted medially whenever possible. Prior to mobilization of the distal esophagus, a large Maloney esophageal dilator was passed by the anesthesiologist and guided into the gastroesophageal junction. The coronary vein and the large periesophageal veins were ligated with #00 silk surture material. The distal end of the esophagus has been mobilized under vision and held up with the aid of a Penrose drain. A generous gastrotomy incision was then performed using the cautery on the greater curvature using stay sutures in order to keep the edges apart. A 28 mm EEA stapler instrument was then inserted into the stomach with the cartridge and anvil approximated to-gether. The instrument guided under vision through the gastro-oesophageal junction as the dilator is slowly withdrawn. The anvil and cartridge then separated, and a #0 silk ligature is passed around the oesphagus approximately 2 cm from the gastroesophgeal junction and tied securely and snugly around the shaft of the open instrument (Fig 2). The anvil and cartridge are then screwed back together, and the instrument is then fired after releasing the safety lever.

This maneuver creates a simultaneously full thickness esophageal resection and an end to end anastomosis of the distal oesophagus with two double rows of staggered circular staples (Fig 3). The anvil is then separated from the cartridge and the instrument is extracted from the gastrotomy incision with gentle rotation. The instrument is then carefully checked for possible retained staples, and more importantly, the resected ring of the esophagus is examined to ensure the completeness of the procedure. The stomach is then irrigated with
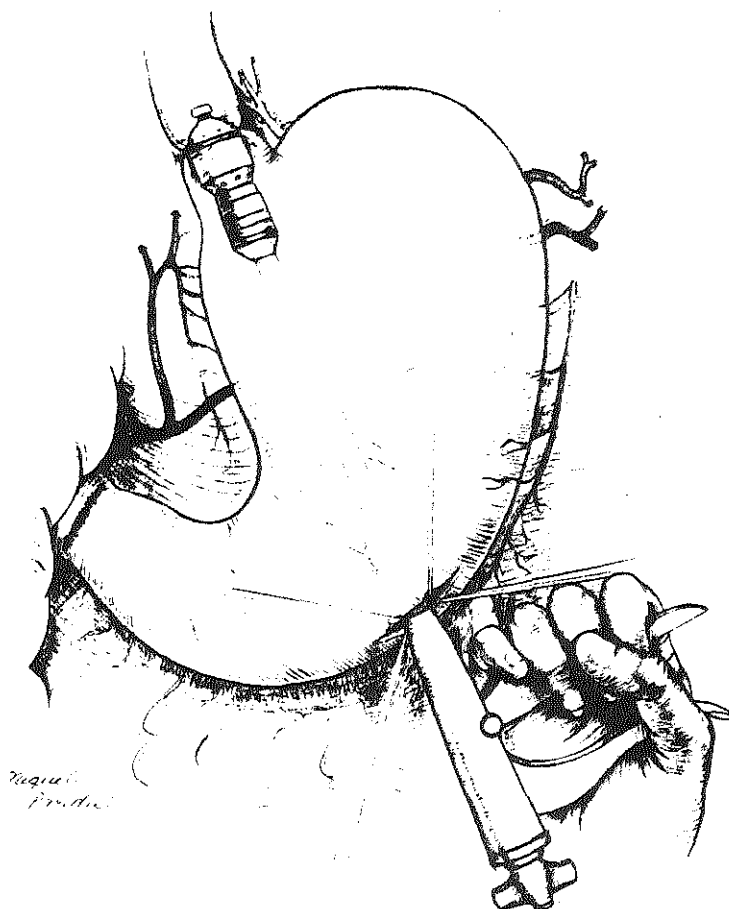
21

Fig 3: Demonstrating the oesophageal resection maneuver using the EEA
        stapler

copius amounts of saline solution and checked for any additional bleeding. Specific attention is paid to the gastric varices, and when found, are ligated in situ using #000 silk suture material. The gastrotomy opening is then closed with a TA-90 stapler or if smaller mouth with a TA-55.

Operative time, vital signs and total blood loss are carefully assessed at this point and if the patient is judged to be stable by both the anesthesiologist and the operating surgeon, a splenectomy is performed if it is technically feasible. Mesenteric vein pressure are performed prior to the splenectomy and immediately after. If the patient remains stable at this point, and blood loss is less than 400 ml, the posterior vagus is then transected between metal clips and a pyloromyotomy is performed. A needle biopsy of the liver is always performed prior to closure of the abdomen. A nasogastric tube is then passed into the antrum and left in that position. The abdomen is closed without drains using nonabsorbable heavy suture material and retention sutures. Postoperatively, the patients are maintained on a chronic regimen of Propranolol.

The combined procedure was performed in only four out of the five patients. It was not performed on the last patient because of the patient's tenuous status during surgery.

Results

Variceal bleeding was totally controlled after the procedure and no anastomotic leaks or disruptions occurred. One patient developed stenosis at the anastomotic site which responded very nicely to esophageal dilatation which was performed three weeks after surgery. In four patients the variceal regression was endoscopically confirmed postoperatively, as well as demonstrated radiographically. Operative time averaged one hour and fifteen minutes. The intraoperative blood loss ranged from 250 ml to 550 ml. One patient who only had the esophageal stapling procedure performed, and was in a Child's C Classification, died ten days postoperatively from combined renal and liver failure. The other four patients who had been followed for up to thirteen months

postoperatively had no evidence of bleeding from any gastrointestinal origin.

Discussion

The cirrhotic patient who presents himself at the hospital today bleeding from esophageal varices can expect to be treated medically first by the use of intravenous vasopressant and balloon tamponade procedures. This patient stands a 70% chance of resuming active bleeding within a few days after the balloon is deflated. This patient will probably continue to be treated medically and even with multIple transfusions, deteriorate to the point that even the bravest of surgeons will be reluctant to operate, especially when ascites, encephalopathy and jaundice are present. Even under the best of circumstances, the operative mortality rate for such emergency procedures of all descriptions range from 40% to 80%. In a series of 146 patients who underwent emergency portocaval shunts, Orloff (1975) reported a 46.6% mortality rate, his operative time averaged 4.2 hours with over 10 units of blood used on each patient. Bleeding promptly stopped in the group of patients, and the portal venous pressure reduced by 1/3, hepatic failure was the cause of death in 55% of the patients. It is apparent by the length of the operative procedure, and the amount of blood used during the patient's hospitalization, that such a procedure would not be feasible for the Jehovah's Witness patient.

In 1967, Warren described the selective distal splenorenal shunt which was designed to reduce the pressure in the portal system while preserving flow to the liver. The procedure was also designed to decompress the gastroesophageal submucosal plexus. The results of this procedure were better than other shunting procedures with regards to liver insufficiencies following the procedure, but it is lengthy and can be bloody as well. Overall survival rates are better in nonalcoholic as opposed to the alcoholic patient. This type of shunt is poorly suited for use in the emergency decompression of varices in elderly patients and patients with refractory ascites, severe impairment of liver function and in patients where blood transfusions could not be employed.

Mesocaval shunts employing a prosthetic graft between the superior mesenteric vein and the vena cava failed to show any superiority over side to side portocaval shunts except from some technical consideration. This type of shunt carries with it a high rate of thrombosis. Emergency mesocaval shunts have been shown to carry with it a 73% mortality rate.

It is generally agreed that there is little, if any, use for prophylactic porto-systemic shunting. Even in patients in whom elective shunts have been performed there was no prolongation in the overall survival time, as compared with the medically treated patients. There has been no changes demonstrated in liver functions that could be related to the decompression procedure.

Because of the high mortality rate associated with emergency shunting procedures, a variety of nonshunting procedures have been attempted to control variceal bleeding when the medical treatment failed to accomplish it. The transthoracic ligation of the bleeding varices offered such a direct approach without interfering with portal flow. Although the advantages of such a procedure is a rapid and early control of the bleeding source, the disadvantages of a thoracotomy, esophagotomy in a sick patient were overwhelming. Orloff reported that only 54% of the patients subjected to the Boerema procedure survived it.

The Milnes-Walker mucosal transection procedure resulted in a similar higher mortality rate of 55%. It also included such complications as esophageal leaks, respiratory failure, severe gastritis with bleeding and mucosal tear.

The Sugiura procedure of gastric devascularization, esophageal diversion, variceal ligation and reanastomosis, while perhaps a good alternative to a decompression procedure, is still a major surgical procedure which is not suited to the actively bleeding, ill cirrhotic patient and certainly not in a Jehovah's Witness patient (Sugiura and Futagawa, 1977).

In 1974, Van Kemmel reported the first esophageal transection and reanastomosis using a Russian staple gun. His results were good even though eight of his twenty-one survivors developed esophageal strictures which responded

to dilatation. There were no anastomotic leaks and no postoperative bleeding. Similar good results were obtained by Johnson in 1977 using the Russian FT-TU stapling gun.

The introduction of the EEA stapler by the U.S. Surgical Corporation was stimulus enough for many investigators to try it in the performance of esophageal transection. In contrast to the early Russian instrument which contained only a single row of 12 hand-loaded metal staples and only a 26 mm cartridge size, the EEA stapler comes in various sizes of the cartridges containing preloaded double rows of 30 staggered staples.

In 1980, Cooperman et al. reported their results with five cirrhotic patients on whom they transected and reanastomosed the esophagus using an EEA instrument; one patient died postoperatively from renal failure, and the other four did well and were discharged without evidence of further variceal bleeding. Wexler (1980), in a similar series, but on a much sicker group of patients, also reported a complete control of variceal bleeding using this method. His mortality rate was much higher, however.

The procedure employing the EEA stapler as well as its modification by Rinecker-Danek (1975) using the GIA instrument without the dividing blade, causes obliteration of the submucosal plexus of veins, as well as the plexus between the muscle layers of the esophagus. It does not, however, interrupt the periesophageal plexus. This fact may not be detrimental if the procedure stands the test of time, and the patients do not continue to bleed. The only procedure which divides all three plexus of veins is the Sugiura devascularization procedure which would not be applicable to the group of patients that we were involved with.

Our experience, as well as other investigators using the EEA technique, shows it to be an easy, quick, simple and very effective way of controlling bleeding esophageal varices. It can be accomplished with less than a unit of blood loss intraoperatively and with an operative time of one hour.

We have added a posterior vagotomy and pyloromyotomy and splenectomy to our

procedure, as well as maintaining these patients chronically on Propanolol (Inderal), because of the special nature of this group of patients which we were involved with. The reasoning behind this approach has been an attempt to combine the initial bleeding control procedure in an intraoperative stable patient, with other modalities which will cause lowering and maintaining a lower portal pressure, as well as decrease the reportedly higher incidence of bleeding from peptic disease seen in cirrhotic patients, as compared with the general population.

It has been our experience that performing a splenectomy in a patient has lowered the portal pressure by 25%. A similar approach to the problem has been attempted by ligating the splenic artery, and further modifications have been employed by Delguercio (1981) even though his technique is somewhat different from ours.

Adding a posterior vagotomy (since we make no attempt to avoid the transection of the anterior vagus during the initial stapling procedure) and a pyloromyotomy adds little to the operative time and the blood loss. It does, however, give an added assurance of decreasing the incidents of bleeding from peptic disease in this group of patients in whom bleeding must be avoided at all costs.

Numerous articles in the medical literature have pointed out the beneficial effect of Propanolol in decreasing variceal bleeding by producing a sustained reduction in portal venous pressure in cirrhotic patients with portal hypertension. The dose of propanolol needed to produce an effective drop in portal pressure must be titrated so that it also produces a drop of approximately 25% in heart rate in those patients. The drop in the cardiac output is thought to cause a decrease in splanchnic blood flow which in turn causes a drop in portal pressure.

We recognize the fact that not every cirrhotic patient who has variceal bleeding is a surgical candidate. For those judged to be too sick to undergo surgery, a few nonoperative modalities are fortunately available. One modality

is the transhepatic percutaneous embolisation of the coronary vein. The other is sclerotherapy through a flexible endoscope. Both procedures can be accomplished without the use of general anesthesia and should be a part of the physician's armamentarium when treating patients with this complex problem.

Our results to date have been encouraging, however, we recognize the fact that we do not have a long-term follow-up on these patients. We have attempted to combine a number of potentially therapeutic modalities within the framework and the limitation imposed upon us by the religious dictates of our patients. We can only hope that other investigators will continue to explore the same or other approaches to this complex problem and provide a larger data base from which concrete conclusions may be drawn in the future.

II-iii Internal Iliac Artery Ligation: Analysis of Fifty Cases

The technique of internal iliac (hypogastric) arterial ligation for the purpose of controlling pelvic hemorrhage has been known for nearly ninety years. Its effectiveness has been proven by many authors. The purpose of this manuscript is to report our experience with this technique in the surgical management of the Jehovah's Witness patient in whom the decrease of intraoperative blood loss is paramount, as well as report on an unusual case where the patient would not have survived without this procedure.

Material and Methods

The data for this report was obtained from our personal surgical experience with over 5,000 Jehovah's Witness patients during the period beginning in September 1973 and ending in March 1983.

Table III illustrates the number of patients on whom ligation was carried out, the primary diagnosis and the complications which occurred following the ligation.

Results

Our experience has demonstrated that no tissue necrosis occurred following the ligation procedures in 50 patients. In only three cases did we notice transient bladder atony. We had no intraoperative mortalities and noticed no significant postoperative complications in this group of patients. We are convinced that the patient (P.E.) which is reported below, would not have survived without employing bilateral retroperitoneal hypogastric arterial ligation.

Discussion

Ligation of the internal iliac arteries to control pelvic bleeding was first performed by Kelly in 1894. Kelly believed the procedure to be bold

Table III

DIAGNOSIS	NUMBER OF CASES	COMPLICATIONS
Carcinoma of the bladder combined cystectomy with ileal loop	4	None
Postoperative bleeding following vaginal hysterectomy	3	Bladder atony developed in one patient
Carcinoma of the bladder. Control of hemorrhage	5	None
Recurrent pelvic tumors (gynecological) with hemorrhage	12	Transient bladder atony developed in two patients
Bleeding from extensive carcinoma of the rectum	2	None
Hemorrhage following childbirth complications	2	None
Carcinoma of the rectum. Combined with abdominal-perineal resection	15	None
Combined with difficult hysterectomies	7	None
Total Number of Cases	50	

Overview of patients undergoing Internal Iliac Artery Ligation and the complications resulting from the procedure.

and dangerous as he felt, as many still do, that this completely shut off the blood supply to the pelvis (Burchell, 1968; Pelosi et al. 1976). Many of the concepts of the physiology of the pelvic circulation were based on experience with the circulatory system in other areas of the body. In the extremities, sudden occlusion of the main blood supply leaves distal tissue with inadequate collateral circulation and leads to tissue necrosis. The physiology of the blood supply in the pelvis is entirely different and ligation of the internal iliacs leads to infrequent and relatively minor complications.

The blood supply to the pelvis is amazingly abundant. The internal iliac artery supplies blood to the wall and viscera of the pelvis, the reproductive organs, the buttocks, and the inner aspect of the thigh. The artery arises at the bifurcation of the common iliac, descends into the true pelvis, and divides into the interior and posterior divisions. The branches of the internal iliac are highly variable. In the most common pattern, the ilio-lumbar, lateral sacral, and superior gluteal arteries spring from the posterior division. The inferior gluteal, internal pudendal, inferior vesicular, superior vesicular, obturator, middle rectal, vaginal, and uterine arteries spring from the anterior division (Pelosi et al. 1976; Grants Atlas of Anatomy, 1978). All of these arteries anastamose extensively, but there are three major collateral systems. They are the lumbar, ilio-lumbars, middle sacral, lateral sacral, and superior hemorrhoidal, middle hemorrhoidal arterial anastomosis (Berlind, 1966).

Burchell, with some elegant work in the 1960's, must be credited for discovering much of what is known about the physiology of the pelvic circulation today. He found that following ligation of the internal iliac arteries, the uterine artery continued to bleed freely after being cut, but that he was able to easily stop the bleeding with pressure alone. He subsequently took pressure and flow readings pre- and post-ligation on a series of patients and discovered there was an 85% drop in pulse pressure, a 24% drop in mean arterial pressure, and a 48% drop in flow post ligation. The ligation changed the pelvic arterial system into a system with flow characteristics very similar to that of a venous system

(Burchell, 1968).

Interestingly enough, with unilateral ligation, the drop in pulse pressure and flow on the contralateral side are minimal. The collateral system is mainly a vertical one with very few horizontal anastamosis. Burchell (1968) followed the pressure and flow readings with arteriography. The arteriography confirmed what the pressure and flow measurements indicated, that the collateral circulation of the pelvis is well developed and ligation of the iliacs deprived no pelvic structures of blood. The blood, rather than going through the internal iliacs to arterial branches to collaterals, reversed direction and went from the collaterals to arterial branches to the internal iliacs. No artery was without adequate blood flow (Burchell, 1968). Several patients were followed up with arteriography several years following bilateral internal iliac ligation. It was found that the iliacs remained occluded and the collaterals did not hypertrophy with time. This indicated that the initial blood supply, following ligation, was adequate, so that no compensatory growth of the collateral system was necessary (Burchell 1968).

There have been several reports in the literature of successful pregnancy following internal iliac ligation. Shinagawa et al. (1981) reported two cases of successful pregnancy following ligation bilaterally of both internal iliacs on infundibulipelvic ligaments. The facts that there is no compensatory growth of collaterals and that a pregnancy can be nourished to successful completion following ligation of the internal iliacs illustrates the vast abundance of the pelvic blood supply.

Complications related to this procedure are infrequent and therefore rarely reported and when they occur are usually mild and transient. Alleged complications are ureteral and vesicular fistulas, necrosis of the buttocks, atonic bladder and circulatory disturbances of the lower extremities (Pelosi et al, 1976).

Sack's review of 48 cases of ligation of the internal iliacs reported transient atonic bladder (4 patients) lasting four days and claudication of

32

buttocks and thighs (1 patient) lasting several weeks that was associated with long standing hypertensive disease (Sack 1973). Lash reported 115 bilateral internal iliac ligations prior to radical hysterectomy for cervical carcinoma. They reported a significantly higher incidence of bladder atony in those patients with iliac ligation compared to controls and a slightly higher rate of ureterovaginal fistulas. The fistulas were all associated with radiation therapy which increases the avascularity of pelvic structures (Lash and MacNerland 1970).

Both Sack and Lash found this procedure to be life saving in the treatment of uncontrollable pelvic hemorrhage and only questioned its use prophylactically and for teaching purposes.

Paploucas (1971) (12 patients), Burchell (1967) (45 patients), Staples (1973) (60 patients), Berlind (1966) (1 patient), and Pelosi (1976) reported no complications secondary to internal iliac artery ligation.

Necrosis is a rare complication and does not occur in a normal pelvis. It only occurs if a number of collateral pathways are destroyed (Burchell 1968). Our population of patients consists mostly of Jehovah's Witnesses who for religious reasons, refuse to accept blood transfusions. In this population, the complications of internal iliac ligation, i.e. bladder atony and fistula formation, which we have seldom experienced, are minor compared with acute tubular necrosis, congestive heart failure, and shock lung associated with hypovolemic shock which can result from severe pelvic hemorrhage and inability to replace blood loss. In patients with severe pelvic hemorrhage who are willing to accept blood transfusions, the above complications are acceptable if the bleeding is severe enough and the complications of hepatitis, transfusion reactions, and acute respiratory distress syndrome which can occur following massive transfusions are considered.

We feel that the benefits of ligation of the internal iliac arteries to control pelvic bleeding far outweigh the complications. If carried out by competent surgeons, the procedure is safe and effective.

CASE REPORT

P.E., a 29 year old Jehovah's Witness female, Para 2, Gravida 2, who on February 11, 1982 delivered a 6 lb 9 oz girl. During the delivery, the patients uterus ruptured and she rapidly went into hypovolemic shock. Because she refused to accept blood transfusions as a part of her medical treatment, she was transferred to Bellflower City Hospital with a hemoglobin of 1.7 gm %. Her blood pressure was 40/70 mm Hg which was partially maintained by the use of shock trousers, pulse was 140 and respirations were 28/min and shallow. Because she was actively bleeding after her arrival via emergency air transport, she was taken to surgery in an attempt to control the bleeding. Because of her extremely critical condition, it was decided not to attempt to perform a hysterectomy but rather to ligate both internal iliac arteries through a retroperitoneal approach. Anesthesia was successfully carried out using intravenous Valium, Ketamine and short acting muscle relaxant. Intraoperative blood loss was approximately 20 cc.

Postoperatively, the patient, who did not receive Fluosol-DA 20%, received intravenous iron dextran, folic acid and intramuscular injections of nandrelone decanoate and B-12. Hydroxyethyl starch was employed for volume expansion. The patient's hospital course was uneventful and she was discharged on the tenth postoperative day with a hemoglobin of 7.9 gms %.

CHAPTER III

GENERAL ANESTHESIA FOR THE ANEMIC PATIENT WITHOUT BLOOD TRANSFUSION.

Our experience includes over 5000 Jehovah's Witness patients who underwent general anaesthesia for major surgery without the use of blood or blood products. These patients tolerated low hemoglobin and hematocrit levels remarkably well. We had one patient who underwent surgery and general anesthesia with a hemoglobin level of 1.7 gms hemoglobin and survived.

Other physicians have reported similar experiences treating Jehovah's Witnesses.

Ott and Cooley (1977), reported a series of 542 patients in whom cardio-vascular surgery was performed without the use of blood or blood products. The bubble oxygenators that were employed were all primed with Ringer's Lactate solutions. Considering the procedures performed and the preoperative status of the patients, the authors produced very good results.

Rush and Eiseman (1967) studied the effects of hemodilution with lactated Ringer's solution in dogs subjected to graded hemorrhages. A four-fold volume replacement for 60% exsanguination resulted in survival, while such replacement after 75% hemorrhage was fatal for the dogs within 24 hours. Moss (1969) subjected splenectomized dogs to sequential 36%, 60%, and 75% hemorrhages. In this series the animals were stabilized after each hemorrhage and relatively more lactated Ringer's was given according to their urinary output. The author emphasized that adequate hemodilution was reflected by good urinary output; all of his dogs were long term survivors.

In view of the above mentioned results of both clinical and experimental studies, it is becoming clear that the blood bank is being grossly overused. On the basis of retrospective analysis, it has been calculated that about 40% of all transfusions are unnecessary. It is the authors opinion that over 85% of all transfusions are not indicated and therefore should not be performed in view of the great risks involved.

Since we primarily deal with Jehovah's Witnesses, we have asked ourselves certain fundamental questions:

1. How do we best prepare a patient that cannot receive blood or blood products for surgery and general anesthesia?

2. What is the best anesthetic technique for patients with low hemoglobin levels?

3. What are the lower limits of oxygen carrying capacity that a patient can survive during general anesthesia?

4. What other choices do we have for severely anemic patients undergoing surgery?

The definitive treatment of acute hypovolemia must be early replacement of intravascular volume, and oxygen supplementation. If the patient shows signs of hypovolemia, indicated by a low systolic blood pressure, increased heart rate, low central venous pressure, or urinary output of less than 1 ml per minute. we like to employ the early use of Hespan (hydroxyethyl substituted amylopectin) Depending on the values of the abovementioned parameters, 500 to 1,000 of Hespan is administered,

This colloid solution is chosen for the following reasons:

1. It is an effective plasma volume expander with characteristics similar to those of human serum albumin.

2. Effects persist for 24-36 hours.

3. It is nearly free of allergic and untoward effects.

4. It has been used for thirteen years at M.D. Anderson Hospital, Houston, Texas, with no anaphylactoid reactions having been observed.

Hespan, marketed by American McGraw Laboratories, is a 6% solution of heta-starch in 0.9% of sodium chloride. If given in doses not exceeding 1500 ml, it has minimum effects on the coagulation mechanisms. This colloid also is a fraction of the cost of albumin.

Next, we give Dextrose 5% in Lactated Ringer's solution 1000 ml followed by

1000 ml of Aminosyn 3.5% - the latter contains all the essential amino acids. Finally, we slowly give a solution that is high in potassium chloride, Electrolyte #75. The regimen assures that the patient has received proper proportions of colloid and crystalloid to maintain intravascular oncotic pressure and electrolyte balance, as well as isotonic interstitial fluid space requirements.

Urinary output is an excellent guide to adequacy or hemodilution in patients not receiving blood or blood products. If the patient is not excreting urine at the rate of a least 1 ml per minute, regardless of other parameters, then more fluids are indicated (e.g. Dextrose 5% Lactated Ringer's Solution). The fluid regimen we have described can usually be completed even in emergency procedures.

In our experience, time is of the utmost importance. Firstly, the patients initial blood loss must be rapidly replaced with crystalloid and colloid solutions. Secondly, if possible, surgery should be delayed long enough for the patient to reconstitute his vascular proteins (albumin), and for the institution of a regime designed to accelerate hemoglobin formation. This regime consists of the administration of intravenous iron dextran and folic acid, and intramuscular injections of Vitamin B-12 and nandrelone decanoate, an anabolic hormone. After a lag period of 24 hours, hemoglobin concentrations rise at an average rate of 0.41 gms per day. Therefore, the more time we have to treat an anemic patient prior to surgery the better anesthetic risk he becomes.

If the patient is hypovolemic and surgery must be performed, the anesthetic induction period is of critical importance. It is important to use an induction agent that does not produce peripheral vaso-dilatation or cardiac depressor. If such an agent is used, this would lead to a severe drop in venous pressure and a reduction in cardiac output with possible fatal results in the severely anemic patient.

We have found that, when inducing anaesthesia in the critically ill or severely anemic patient, the administration of a combination of Diazepam and Ketamine has advantages in that, not only are amnesia and hypnosis produced, but

also a strong analgetic effect is caused. Furthermore, Ketamine is a myocardial stimulant that raises blood pressure, cardiac output, and heart rate but does not depress respiration. The occurrence of emergence delirium, hypertension and tachycardia are undesirable effects that may be produced by the drug. The first of these negative characteristics can be largely blocked by Diazepam 5 to 15 mg intravenously, as first demonstrated by Dundee and Lillburn (1977). Zsigmond et al. (1974) have shown that tachycardia and hypertension are caused by elevated catecholamine levels, primarily of norepinephrine, and that this can also be blocked by Diazepam.

The patient is preoxygenated and while breathing 100% oxygen, small increments of Diazepam (5 to 15 mg total dose) and Ketamine (50 to 75 mg total dose) are slowly administered by the intravenous route. When induction is complete, rapid intubation is performed with the aid of a short acting depolarizing muscle relaxant. We have found that when Ketamine is used in this fashion, there is little or no cardiovascular stimulation.

After induction, most patients require minimal amounts of inhalational anesthesia. We use an oxygen-isofurane technique. We have now used this drug on several hundred patients and like it for several reasons. Isofurane has a lower blood-gas partition coefficient (1:4), than Enflurane (1:9), or Halothane (1:3.6). This means that the depth of anesthesia can be changed more rapidly and with greater safety. Elimination from the lungs is also more rapid, and the patients are usually able to respond to commands within 12 minutes after the anesthetic has been discontinued. Secondly, Isofurane has relatively little effect on the myocardium. In normocapnic patients, 1 to 2 MAC Isofurane does not significantly decrease cardiac output, whereas, over the same range (1 to 2 MAC), Halothane and Enflurane decrease output by 20 to 30%.

In addition to an absence of myocardial depression under isofurane, no increased incidence of ventricular arrythmias is noted under the influence of this agent. Although there is a decrease of 15 to 20 mm Hg in systolic arterial pressure, this decreases left ventricular work and myocardial oxygen consumption

by up to fifty percent at deeper levels of anesthesia. This is obviously beneficial for our anemic patients. The 20% increase in heart rate, is abolished by moderate doses of narcotics such as 0,1 or 0,2 mg of Fentanyl. For the above reasons, Isofurane is our choice for patients with impaired myocardial perfusion and/or function (CHF). We are so pleased with this agent that we use it almost exclusively in all our adult patients, anemic or not.

Muscular relaxation under anesthesia is secured by the use of an intravenous suxamethonium (2 mg/ml). A supplemental narcotic is often given depending on the patients intraoperative condition. We like Fentanyl because of its rapid onset, short duration of action and lack of cardiac depressant properties. As is the case with Diazepam it also prevents the adverse hyperdynamic cardiac response to a ketamine induction. There is also evidence that it blocks the stress hormone responses of surgical trauma. Laryngeal and tracheal reflexes are depressed facilitating the intraoperative and postoperative management of the intubated patient. In short, Fentanyl supplementation provides a smooth and safe anesthetic which can result in an awake and pain free patient in the immediate postoperative period.

In our experience with over 5,000 patients of the Jehovah's Witness faith, we found very few who needed blood or blood products. It seems clear that most adult patients can undergo rapid loss of 1000 to 2000 ml of blood. They will not go into irreversible shock if hemodilution is adequate. Cellular elements are rarely needed even after extensive blood loss of 2000 ml or more. Leukocyte and platelet reserves are such that there is a rapid outpouring of each into the circulation during and immediately after any significant bleeding. In our experience, thrombocytopenia and leukopenia are rarely a problem.

The ultimate survival of the patient is determined by the relationship between a decreasing oxygen carrying capacity of blood and myocardial oxygen need. The extent to which a patient can compensate for anemia is dependent upon his reserves. The patient with a low hemoglobin has a decrease in blood viscosity, a shift in the oxyhemoglobin dissociation curve to the right, an

increased oxygen extraction by various organs, an increased erythropoietin production, an increased vasomotor response and an increased cardiac output. This increase in cardiac output is only possible if the patient is hemodiluted to normovolemia. Because heart rate changes only slightly with adequate fluid replacement, the increase in cardiac output is due to an increase in stroke volume associated with increased venous return. If there is an increase in heart rate with a small increase in cardiac output, then the patient is still probably hypovolemic.

Andrews et al. (1980) state that coronary blood flow is normally highly privileged to prevent any fall in coronary sinus pO2. This increase in coronary blood flow is out of proportion to relative increases in cardiac output in response to anemia, as long as the hematocrit does not fall below 20%. These authors further state that increased tissue extraction of oxygen and shift of oxy-hemoglobin dissociation curve to the right occur at hematocrits below 20%, or when hemodilution is associated with hypovolemia. Furthermore, it appears that at hematocrits in this range there is a more homologous distribution of oxygen to tissues.

As previously mentioned, myocardial performance is the other key determinate in maintaining adequate tissue oxygenation. The heart normally utilizes 65 to 70% of the oxygen available in coronary arterial blood, the brain extracts one-third and the kidneys less than 10%. Therefore, oxygen to the myocardium is the weakest link in allowing our patients to respond to anemia. If hemodilution is inadequate or if started too late, the return of stagnant peripheral, hypoxic, and acidotic blood into the circulation lowers cardiac output and aggravates the situation further. A negative cycle can be started in which a hypoxic myocardium leads to further increases in hypoxia due to decreased cardiac output. If this cycle is believed to be in effect or even pending, Sodium Bicarbonate, high dose steroids, and digitalization may be indicated if the patient can not receive blood.

The availability of Fluosol-DA 20% for increasing the blood's oxygen carrying

capacity may greatly help in the preoperative preparation of the Jehovah's Witness patient. Our results with nine anemic patients with hemoglobins of 8.0 gms or less were very encouraging. All nine patients tolerated surgery although the most severly anemic patient, who had a haemoglobin concentration of 1,9 gm%, died on the fifth postoperative day from complications unrelated to the Fluosol therapy. Another patient, aged 75 years, (mean Hb = 6.2 gm%) with severe cardio-pulmonary disease died three weeks postoperatively. This again was unrelated to the Fluosol therapy. This substance as well as a new generation of perfluorocarbons called Fluosol-DA 35-2, which can be stored in an unfrozen state and used without the need of high PaO2 tensions, could greatly improve our ability to treat the severely anemic patient.

In conclusion, we believe blood and its products have been overused in the past and are still presently being overused. Furthermore, we have demonstrated viable alternatives to blood therapy in the anemic patient who needs surgery.

CHAPTER IV

METHODS OF AVOIDING BLOOD TRANSFUSION

IV-i Intraoperative reinfusion

Introduction

In spite of the current interest in intraoperative reinfusion and the acknow-
ledged benefits of the autologous versus homologous transfusions, this approach
towards blood conservation and minimizing the risks inherent to blood trans-
fusions (Table IV) has not received the recognition which it properly deserves.
Reluctance by surgeons to use this technique is undoubtedly due to the confusion
which still exists in the literature regarding the possibility of complications
in using this procedure. Widely divergent hematological abnormalities in the
form of various coagulopathies and hypofibrinogenemia still appear in medical
communications.

It is the purpose of this part of the thesis to report and extensively
discuss our experience with .this technique in the past seven years. Our
experience involved a total of 758 patients. Although the majority of this
experience involved the cell saver apparatus (manufactured by the Hemonetic
Corporation), we have also had some experience with the ATS-100, (manufactured by
Bentley). We will attempt to discuss each separately, as well as compare their
performance.

Materials and Methods

Seven hundred and fifty eight patients undergoing cardiac, orthopaedic,
thoracic, urological and general surgical procedures have been subjected to
intraoperative autotransfusion when this modality of treatment was acceptable to
the individual patient. Three hundred and seventy-four patients had open heart
procedures, three hundred and thirty-one had orthopaedic procedures and fifty-

Table IV: POTENTIAL PROBLEMS IN TRANSFUSION THERAPY

Type	Cause	In Vivo	Symptoms	Prognosis	Action	Prevention
Hemolytic Reactions						
Immediate	Lysis of donor cells by anti-body	Direct attack on transfused red cells by recipient anti-body and complement with intra-vascular and extravascular destruction. Hemoglobin is released	Pain at infusion site; flank pain; fever (with or without chills); chest pain; hypo-tension/shock; dyspnea; flush-ing; excessive oozing of blood; hemoglobinuria	Life-threat-ening, sometimes fatal	Stop trans-fusion; give mannitol or furosemide; maintain urinary flow	Careful adherence to testing and transfusion protocols. Start trans-fusion slowly and ob-serve patient closely for first 15 minutes
Delayed	Lysis of donor cells by anti-body 1−2 weeks after transfusion	A prior expo-sure to antigen produced no detectable antibody. A second stimu-lus (transfu-sion) pro-duces anti-body which lyses the still circulating crossmatched cells	Decreased hemo-globin; increased bilirubin; posi-tive direct anti-globulin; anuria or oliguria; hypo-tension/shock	Usually mild, but can be life-threatening	Identify causative factors; sup-port the pa-tient with all mea-sures, as in an immedi-diate reac-tion, if necessary	Thorough investigation of all suspected anti-bodies. Proper use of universal donor blood
Interdonor	Lysis of donor cells by previ-ously trans-fused antibody	Destruction of some or all of the new donor cells	Mild to severe	Mild (de-pends on serologic character-istics of the antibody) to severe with anuria	Stop trans-fusion	Do not transfuse blood containing hemolytic antibodies. Use PRBC with most of plasma removed.
Lysis of Recipient Cells by Passively Antibody	Antibody in donor plasma destroys recip-ient red cells	Small amount of antibody bound due to excess amount of antigen. Antibody di-luted in pa-tient's plasma	Mild to none	Mild to severe	Stop trans-fusion	Use packed red blood cells

Table IV: POTENTIAL PROBLEMS IN TRANSFUSION THERAPY (CONTINUED)

Type	Cause	In Vivo	Symptoms	Prognosis	Action	Prevention
Nonhemolytic Reactions						
Febrile	Antileukocyte antibody; anti-platelet antibody, anti-serum protein antibody	Plugging of pulmonary vessels by leukocyte antigen-antibody complexes; focal vascular injury causing fluid exudation into lung tissue. Damage releases pyrogens	Mild: chills, fever, headache, myalgia, nausea Severe: hypotension, chest pain, dyspnea, vomiting	Usually not life threatening, although symptoms can be severe	Stop transfusion; anti-pyretics, antihistamines, support patient, investigate cause (full workup)	Use leukocyte poor or frozen red blood cells
Allergic	Allergens in transfused blood (IgE antibody); history of patient allergy; transfusing IgA to IgA deficient patients	Transfused antigen binds to mast cells, causing disruption and release of histamine and serotonin	Mild: urticaria, facial swelling Severe: dyspnea, hypotension, laryngeal edema, substern-chest pain, shock	Mild to life-threatening	Stop transfusion; treat life threatening symptoms; diphenhydramine (parenteral), epinephrine, corti-costeroids	Use frozen deglycerolized or washed red cells; use IgA deficient plasma
Circulatory Overload	Blood volume too large for pumping action of heart	Congestive heart failure, pulmonary edema	Tightness in chest, dyspnea, basilar rales, diaphoresis	Good if treated early	Slow or stop transfusion, diuretics, rotating tourniquets, patient in sitting position, administer oxygen, monitor vital signs	Give PRBC, monitor transfusion, give slow transfusions in divided units
Contaminated Blood	Bacterial growth (usually gram negative)	Produces exotoxins	Fever, shaking chills, abdominal pain, pain in extremities, vomiting, bloody diarrhea, hypotension	Poor	Stop transfusion, parenteral antibiotics, vasopressors, corticosteroids, fluids, electrolytes	Aseptic collection technique proper and continuous refrigeration of blood from collection to transfusion, careful visual examination of blood prior to transfusion, use only inline blood warmers

44

Table IV: POTENTIAL PROBLEMS IN TRANSFUSION THERAPY (CONTINUED)

Type	Cause	In Vivo	Symptoms	Prognosis	Action	Prevention
Nonhemolytic Reactions						
Air Embolism	Air introduction into venous system during transfusion	Blood becomes frothy and cannot be pumped by the heart	Dyspnea, cyanosis, shock, cardiac arrest	Poor	Stop transfusion, position patient on left side with head lowered, treat shock/cardiac arrest	Avoid introduction of air into tubing, do not change transfusion set intraprocedure
Lysis (Nonhemolytic)	Mechanical trauma, osmotic damage, thermal extremes	Hemolysed red cells	Elevated bilirubin	Good—depends on extent of damage	Stop transfusion, support patient, correct problem	Avoid obstruction of blood flow (check for kinked tubing), use only isotonic normal saline as starter solution, use properly set blood warmers and avoid extremes of temperature during storage and handling

three had miscellaneous procedures. These patients were treated in two small community hospitals with a total bed capacity of 375 beds. In 46 patients, the ATS-100 was either actively used or kept on a standby basis. The rest of the patients were treated by the cell saver.

We will examine and report at length on the first 100 orthopaedic procedures, which we included in this series (Table V). Nine patients were omitted due to lack of data. ProTime, PTT, 23 DPG, and electrolytes were estimated pre- and postoperatively and found to be within normal limits. The average red blood cell recovery in the first 100 patients was a disappointing 43%, as measured by the hematocrit value. In the next 131 patients, the harvesting rate increased to 61%. This was accomplished by modifying our techniques to include ringing out sponges, keeping the suction tip at an angle and always in the wound, and the suction kept as low as possible. Our average total blood loss per case has continued to decrease after employing the electrocautery device almost exclusively in order to perform the surgical procedures. The scalpel was only used to make the initial skin incision. Spinal anesthesia was employed whenever possible and hypotension was used in 83% of the cases, the systemic blood pressure was maintained at 80 plus or minus 5 mmHg. Of the first group of patients, only six required supplemental homologous transfusions in the post-operative period. In the next 131 cases, only two patients needed supplemental homologous transfusions. It is interesting to note that as our techniques of minimizing blood loss improved, the cell saver was used only as a standby modality in over 52% of the patients. Since the amount recovered during the surgical procedure was so small, it was hardly worthwhile reinfusing the harvested blood back to the patient. The experience obtained in other surgical specialities using this method, and the cell saver, have paralleled the reported orthopaedic experience. Only one case of hepatitis was reported where the cell saver or the ATS-100 were used exclusively.

Table V: **Intraoperative Autologous Transfusion in 43 Spinal Fusions**

Name	Operation	EBL (Estimated blood loss)	Cell Saver (Recovery)	Pre-Op H & H	Post-Op H & H
T.B.	Anterior spinal fusion with Zilke inst. T11-L5	800 cc.	350 cc.	14.0/40.3	13.4/39.7
K.M.	Posterior spinal fusion with H.I. T5-L3; rt. posterior iliac crest bone graft	700 cc.	250 cc.	12.9/38.4	12.5/34.8
E.T.	Posterior spinal fusion with H.I. T11-L4 rt. iliac crest bone graft — single distraction rod	No data	No data	12.2/36.0	11.6/33.1
C.P.	Posterior spinal fusion with Harrington inst.	800 cc.	250 cc.	16.7/48.0	16.6/48.0
A.B.	Posterior spinal fusion with Harrington inst. T2-12	900 cc.	600 cc.	13.6/42.6	13.5/42.3
J.O.	Posterior spinal fusion with Harrington inst.	500 cc.	300 cc.	14.2/41.8	13.5/40.2
S.M.	Posterior spinal fusion.with Harrington inst.	800 cc.	250 cc.	11.7/34.5	11.6/32.6
J.T.	Posterior spinal fusion with Harrington inst.	750 cc.	300 cc.	13.6/39.4	15.8/45.9
A.S.	Posterior spinal fusion with Harrington inst.	650 cc.	250 cc.	13.6/38.4	12.7/36.6
D.Z.	Posterior spinal fusion with Harrington inst.	500 cc.	250 cc.	No data	14.1/42.2
L.F.	Posterior spinal fusion with Harrington inst.	900 cc.	500 cc. plus 1 unit bank blood	11.8/35.4	11.1/32.9
D.G.	Posterior spinal fusion with Harrington inst.	400 cc.	250 cc.	12.9/38.2	12.1/36.2
K.A.	Posterior spinal fusion with Harrington inst.	450 cc.	150 cc.	14.2/42.6	13.1/58.8
V.D.	Posterior spinal fusion with Harrington inst.	1100 cc.	500 cc.	13.8/41.4	13.2/40.0
M.S.	Posterior spinal fusion with Harrington inst.	600 cc.	300 cc.	13.6/40.4	12.5/37.9
C.B	Posterior spinal fusion with H.I. T10-L4; rt. iliac crest bone graft	375 cc.	175 cc.	12.8/38.6	12.7/38.4
W.C.	Posterior spinal fusion with H.I. — bone graft — T3-11	600 cc.	300 cc.	13.1/37.7	12.6/37.1
D.G.	Posterior spinal fusion transverse process to transverse process bilat., L2-3-4	500 cc.	250 cc. plus 1 unit packed cells (bank)	11.6/33.9	12.3/38.4
T.B.	Posterior spinal fusion with H.I. T3-L1 with single Harrington distraction rod. Rt. posterior iliac bone graft	1200 cc.	500 cc.	14.2/42.4	13.3/38.8
K.W.	Posterior spinal fusion T5-L2 with autogenous bone graft & application of transverse tx	800 cc.	300 cc plus 1 unit whole bank blood	13.0/39.2	14.2/42.8

Table V (contd): **Intraoperative Autologous Transfusion in 43 Spinal Fusions**

Name	Operation	EBL (Estimated blood loss)	Cell Saver (Recovery)	Pre-Op H & H	Post-Op H & H
M.P.	Posterior spinal fusion with Knodt rod	1000 cc.	500 cc.	14.6/43.0	14.6/41.2
C.H.	Posterior spinal fusion with H.I. T3-L4, distraction rod #1253 & 1254 hooks direct trans. tx. T7-9 rt.; Knodt direct trans. tx. L2-3 rt. posterior iliac bone graft	650 cc.	300 cc.	13.0/40.0	11.9/35.5
S.W.	Posterior spinal fusion with H.I. T4-L1 with direct trans. tx. T7-9	600 cc.	250 cc.	13.4/38.3	13.1/37.6
C.K.	Posterior spinal fusion with autogenous bone graft from lt. iliac crest, T12-L5	800 cc.	300 cc.	14.1/40.2	12.2/36.1
K.H.	Posterior spinal fusion with H.I. and trans. tx.; T5-L4 with autogenous bone graft correction of thoracic and lumbar curve	900 cc.	400 cc.	12.4/35.1	13.1/39.1
P.D.	Posterior spinal fusion with Harrington inst.	500 cc.	350 cc.	12.8/37.9	11.6/34.4
R.M.	Posterior spinal fusion with Harrington inst.	1300 cc.	450 cc.	15.4/45.3	14.7/43.9
L.F.	Posterior spinal fusion with Harrington inst.	800 cc.	500 cc.	13.8/40.0	12.0/39.7
M.M.	Posterior spinal fusion T4-L4; direct trans. tx. T7-9	1400 cc.	225 cc. C.S. whole blood 1000 cc.	13.5/38.0	15.4/46.8
R.O.	Posterior spinal fusion with Harrington inst.	850 cc.	600 cc.	13.7/41.6	12.9/38.4
H.R.	Posterior spinal fusion with Harrington inst.	800 cc.	350 cc.	14.5/43.9	13.0/38.5
A.F.	Posterior spinal fusion with Harrington inst.	800 cc.	350 cc.	11.8/34.3	10.4/30.8
W.J.	Posterior spinal fusion with Harrington inst.	700 cc.	300 cc.	15.0/46.9	14.2/43.0
C.D.	Posterior spinal fusion with Harrington inst.	225 cc.	150 cc.	13.8/39.8	11.4/34.0
S.P.	Posterior spinal fusion with Harrington inst.	1000 cc.	500 cc.	14.3/42.8	12.6/35.9
D.B.	Posterior spinal fusion with Harrington inst.	700 cc.	350 cc.	13.3/39.0	10.9/32.0
B.N.	Posterior spinal fusion with Harrington inst.	150 cc.	80 cc.	14.7/43.4	13.8/39.9
P.M.	Posterior spinal fusion with Harrington inst.; trans. tx. and laminectomy of L4	3500 cc.	1250 C.S. plus 2000 cc. whole blood	15.6/46.3	14.4/43.1
T.M.	Posterior spinal fusion with H.I.; laminectomy of T9 & 10	250 cc.	100 cc.	13.0/38.0	11.9/35.3
D.R.	Posterior spinal fusion with H.I. T4-L2	1000 cc.	250 C.S. 2 units whole blood	13.7/39.9	12.5/37.0
M.W.	Posterior fusion, C1-2	250 cc.	100 cc.	14.1/41.9	13.8/41.6
S.L.	Posterior spinal fusion with Harrington inst.	1500 cc.	500 cc.	14.1/40.0	12.6/35.0
A.B.	Posterior spinal fusion with H.I. T8-L4	800 cc.	300 cc.	13.8/39.5	13.1/37.5

Table V (contd): Intraoperative Autologous Transfusion in 17 Lumbar Laminectomies

Name	Operation	EBL (Estimated blood loss)	Cell Saver (Recovery)	Pre-Op H & H	Post-Op H & H
B.A.	Lumbar laminectomy Gill procedure, posterior lateral spinal fusion rt. iliac crest	200 cc.	125 cc.	14.6/43.0	12.1/35.2
R.S.	Complete laminectomy L4 lateral transverse process fusion	2000 cc.	750 cc.	15.3/45.0	13.8/41.4
K.G.	Lumbar laminectomy	500 cc.	300 cc. plus 1 unit W.B. bank	12.1/37.5	13.9/41.9
J.B.	Lumbar laminectomy with spinal fusion L5-S1	400 cc.	250 cc.	15.2/47.0	13.2/37.5
D.C.	Lumbar laminectomy L5-S1 bilat. with fusion transverse process L5-S2	300 cc.	150 cc.	14.3/42.6	11.1/32.1
D.L.	Lumbar laminectomy with biopsy, L4-5 disc and vertebral body	600 cc.	300 cc.	14.7/44.6	13.7/42.2
J.D.	Lumbar laminectomy post. and late fusion L4-S1	500 cc.	250 cc.	17.1/47.3	12.2/35.0
E.Y.	Lumbar laminectomy L5	600 cc.	200 cc.	12.7/38.0	11.5/34.5
D.W.	Lumbar laminectomy with P.S.F. L5-S1	700 cc.	250 cc.	16.3/46.8	11.6/34.0
P.C.	Lumbar laminectomy with P.S.F.	200 cc.	100 cc.	11.6/34.2	No data
W.E.	Lumbar laminectomy	600 cc.	350 cc.	13.8/40.5	11.1/32.8
C.P.	Lumbar laminectomy with P.S.F. L4-S1	500 cc.	250 cc.	13.5/40.9	Two days P.O. 9.5/27.7
E.T.	Lumbar laminectomy with Weiss spring	250 cc.	125 cc.	12.3/36.0	11.0/32.7
E.P.	Lumbar laminectomy	300 cc.	150 cc.	11.7/34.2	9.6/28.3
D.B.	Lumbar laminectomy with Knodt rods L4-S1	1000 cc.	500 cc.	15.7/44.2	11.6/32.4
T.S.	Lumbar laminectomy, bilat. L5-S1	400 cc.	100 cc.	15.7/44.8	14.4/40.6
M.S.	Lumbar laminectomy, bilat. Nue rod and foraminotomy	400 cc.	200 cc.	10.9/31.5	9.6/28.9

Intraoperative Autologous Transfusion in 22 Total Hip Replacements

Name	Operation	EBL (Estimated blood loss)	Cell Saver (Recovery)	Pre-Op H & H	Post-Op H & H
L.B.	Rt. total hip replacement	250 cc.	100 cc.	12.9/37.5	13.1/40.0
D.S.	Rt. total hip replacement	200 cc.	100 cc.	12.9/37.9	12.8/38.8
E.C.	Rt. total hip replacement	200 cc.	100 cc.	9.2/27.1	8.7/25.4
L.P.	Lt. total hip replacement	400 cc.	No data	11.3/35.3	9.5/28.7
P.B.	Lt. total hip replacement	400 cc.	No data	11.8/34.8	7.6/21.9
A.R.	Rt. total hip replacement	400 cc.	No data	10.9/32.0	10.6/32.0
K.R.	Lt. total hip replacement	No data	No data	13.3/40.0	12.6/35.7
M.A.	Total hip replacement	600 cc.	300 cc.	11.8/35.4	11.3/34.1
T.H.	Lt. total hip replacement	800 cc.	250 cc.	15.9/49.2	14.9/45.2
W.H.	Rt. total hip replacement	500 cc.	200 cc.	14.9/44.3	12.0/36.8
C.T.	Rt. total hip replacement	300 cc.	No data	13.9/39.0	11.9/33.9
J.M.	Lt. total hip replacement	500 cc.	250 cc.	13.5/40.5	12.8/38.4
R.P.	Lt. total hip replacement	500 cc.	200 cc.	14.9/44.1	13.4/39.5
G.H.	Rt. total hip replacement	1000 cc.	350 cc. with 1 unit whole blood	10.9/31.7	13.1/39.5
R.R.	Rt. total hip replacement	700 cc.	300 cc.	16.0/48.2	15.7/47.6
J.D.	Lt. total hip replacement	500 cc.	200 cc.	15.0/44.0	14.4/42.6
V.K.	Rt. total hip replacement (revision)	600 cc.	200 cc.	11.5/33.9	12.0/37.6
R.L.	Lt. total hip replacement	200 cc.	100 cc.	13.8/42.3	11.3/33.2
G.M.	Lt. total hip replacement	300 cc.	150 cc.	11.3/33.9	9.9/32.5
C.H.	Rt. total hip replacement	200 cc.	100 cc.	14.9/43.1	12.3/38.5
W.T.	Lt. total hip replacement	500 cc.	250 cc.	10.2/29.6	7.4/22.5
R.S.	Rt. total hip replacement	No data	No data	12.7/35.8	12.3/36.6

Discussion

Intraoperative reinfusion as a viable concept should be credited to Highmore who, in 1874, suggested that the patient's own blood could be given back to him after being defibrinated and warmed. He proposed that the method of administration would be via a Higginson's syringe and a transfusing pipe. Nonoperative autotransfusion was advocated originally, however, by Blundell (1818), when he used the technique in severe postpartum hemorrhage patients. In 1885, Duncan, using phosphate of soda as an anticoagulant, salvaged 100 cc of whole blood during a surgical amputation of a leg and reinfused it into the patient who apparently did not suffer any ill effects. Encouraged by his first triumph with this technique, Duncan continued to use it on several other patients, although he did not report it. In 1914, Ties reported his experience in the treatment of ectopic pregnancies. By 1922, a total of 164 cases of intraoperative reinfusions were accumulated and analyzed by Burch. The first report of employing this technique in the United States came in 1931 when Lockwood used it in performing a splenectomy for Banti's syndrome. Since that first American literature report, the technique has been used in the treatment of hemothorax, ruptured spleens, carbon monoxide intoxication, amputations, ectopic pregnancies, abdominal wounds, stab wounds of the heart, neurological and orthopaedic procedures, multiple trauma, and chest and cardiac surgery.

In 1970, Klebanoff, who two years earlier introduced the disposable autotransfusion unit (made by Bentley), reported that in over 1,000 cases of documented autotransfusions in the Western literature not a single death was directly attributed to the autotransfusion itself. There was, however, no standardization of this method by which the blood was collected, processed, and reinfused. It was only with the emergence of high quality medical plastics and improved medical engineering that it was possible to develop a high quality and reasonably reliable unit to perform such a task with uniformed results.

In the late 1960's, for many various reasons, the demand for homologous blood increased sharply. Among them were the large number of Vietnam war injuries, the

rapid advancement in thoracic and open heart surgeries, and the development of the rapid emergency transport system. This has resulted in an increased demand for large quantities of blood for trauma cases, as well as for patients for elective surgery. Despite the enormous growing need for blood, the availability of it was drastically cut when the use of paid donors was curtailed and better screening methods eliminated diseased donor's blood. To compound the problem, federal and state laws regarding blood transport became considerably more restricted. The shortage of blood has again reintroduced the concept of autotransfusion.

In 1968, the Bentley (ATS-100 device) became the first commercially available autotransfusion apparatus to appear on the American market. It was the first attempt in adapting a variable speed roller pump and a cardiotomy reservoir with a filter of nylon mass, two being for suction lines and reinfusion lines, as well as a suction device. Today an alarm system that monitors the blood level in the reservoir is also available in order to prevent the potential development of air embolisms. Utilizing this device, all sequestered blood that is not grossly contaminated can be aspirated and reinfused at a rate which is only limited by the size of two venous catheters that provide a portal of entry into the patient's vascular system. Before using the ATS-100, the patient must be completely heparinized using 300 units/kg of body weight. Even though it has been implicated in causing fatal air emboli, this complication can be avoided by the use of a trained technician and an alarm system. This device can be quickly set up and is particularly useful in cases where blood loss is rapid. The blood is returned back into the patient in a filtered, but otherwise unaltered, state. This fact is an important one especially when large amounts of blood are lost and clotting factors may not be readily available for replacements. The author has used this technique on 47 patients without complications.

In the late 1970's, the cell saver apparatus (manufactured by the Heonetic Corporation) became widely used and popular. It works in the following manner: the blood is aspirated from the surgical field via a suction tip left always at

the operating site. It goes into a double lumen heparin washed tube after passing through a filter. The blood is then pumped into a holding reservoir. Fat tissue particles, platelets, and white cells are filtered out; 1,000 cc of normal saline is used to wash the filtrate which is pushed into a centrifuge by a roller type pump. Plasma, myoglobin, heparin, free hemoglobin, and clotting factors are removed. The washed red cells are packed and given back to the patient. The author has been able to return approximately 61% of the shed red cells back to the patient by employing low suction and meticulous techniques. No changes in ProTime, PTT, 23 DPG's and other tests which have been performed were observed. Seven hundred and fifty eight patients over the past four years have been successfully treated by the author with this apparatus. Three hundred and seventy-four were cardiac cases, three hundred and thirty-one orthopaedic cases and fifty-three were classified in the general surgery category. Part of the orthopaedic group will be discussed in detail later on in this chapter. No deaths in this group of patients were directly attributable to the use of the cell saver. When using this apparatus, one has to monitor the patient's state of hydration very carefully because he may have a normal hematocrit, but still be hypovolemic. Unlike the ATS-100, the cell saver is thought to be easier to operate, less versatile, and requiring more colloidal support. To be cost effective, the average minimum of units of blood needed to be reinfused are 4.5 for the Bentley and 3.7 for the cell saver. A report from Massachusetts General Hospital (1981) suggested that the net saving per operation, per patient was $115 with the Bentley and $176 with the cell saver.

Some degree of cell damage is inflicted by both devices in the process of harvesting the cells. With the Bentley, one can observe a rise in plasma free hemoglobin, which is probably due to the suction roller pump compression interface with air and tissue, as well as turbulence in the tubing reservoir and filters. The cell saver gives a much lower level of plasma free hemoglobin, which is due to the washing. Stillman (1980) has shown that protection against red cell damage can be achieved in dogs by the use of methylprednisolone.

Hemoglobinuria, per se, does not diminish renal function which is more influenced by hypotension, acidosis and hypovolemia.

A major concern in the past has been the possible detrimental effect of the ATS-100 on coagulation mechanisms and the possibility of initiating disseminated intravascular coagulopathy. It is, however, difficult to point the finger at this system because most ATS patients, as reported by other investigators, have received large amounts of homologous blood as well as having superimposed insults of severe tissue trauma, shock and acidosis. Platelet aggregation has caused some reduction in platelet count, but this has not been clinically significant. Decrease in fibrinogen levels and increase in ProTime and PTT time can occur which reflects some loss of clotting factor, dilutional effects and systemic heparinization which is often incompletely reversed at the end of the operation. The cell saver avoids reinfusion of activated clotting factors but at the expense of washing out other factors in the discarded plasma.

The optimal anticoagulation which prevents microemboli and potentially disastrous respiratory failure seems to be systemic heparinization and the addition of ACD or CTD to the suction system.

Even though Klebanoff demonstrated in 1970 that grossly contaminated blood could be safely reinfused into dogs without ill effects, there has been a continued reluctance on the part of surgeons to reinfuse blood which has been contaminated by bowel content. We found it necessary to reinfuse contaminated blood using the cell saver and observed few, if any, problems - Sepsis is obviously easier to treat than rigor mortis. Broad spectrum antibiotics regimen is given to all such patients.

For the sake of completeness it is only fair to mention that a similar cell washing device, manufactured by IGM, and utilizing a Sorenson's collection system is also on the market today. We have had no personal experience with this apparatus, but, regarding its use in the intraoperative reinfusion, it has been observed that it is a rather large, not easily movable, piece of equipment, and that a collection system must, therefore, leave the room for a washing process.

When this machine is used in a busy operating room, delays and potential fatal complications can occur through clerical errors.

The Jehovah's Witness patient's view on the use of intraoperative auto-transfusion is uniform in the objections to the storage element of the process, no matter how short the period of time. Yet, there is always an element of storage in any extracorporeal circulatory device and that must always be explained to the patients. Some have accepted this method as a conscious matter, while others have rejected it. We have had a number of patients who refused to undergo cardiac surgery because they could not accept the concept of their blood circulating through a pump oxygenator. As a general policy, we have never tried to change the religious view points of this group of people, but rather work to improve and modify the available hardware to minimize storage time and to keep blood constantly circulating.

There is no question that homologous blood has many disadvantages. It is expensive, not always available, and overly utilized. It can cause febrile reaction, isoimmunization, syphillis, malaria, bacterial infection, Epstein-Barr virus, Australian antigen positive virus, negative hepatitis producing virus, major histocompatibility reaction, vascular overload, and hemosiderosis. The average unit of blood sitting on the shelf in the blood bank has a high concentration of potassium, ammonia and hydrogen ions in the plasma. The red cells are low in 23 DPG. Also larger than normal accumulation of cellular debris is found in stored blood.

Blood conservation efforts along many fronts, of which intraoperative reinfusion is only a part, will help our dependency on the blood bank and assure that blood is available to the people who want it when it is needed. If we can only continue to remind ourselves that the best blood we can give a patient is his own, and that transfusing a patient with a unit of whole blood is analogous to giving a patient a unit of liquid organ transplant. Then and only then will we begin to look at the patient as being his own blood bank and treat him as such. Transfusing an anemic asymptomatic patient makes the doctor feel

better and the medical chart look good in an audit situation, but the patient is subjected to needless, extensive, and potentially hazardous treatment.

IV-ii The use of intravenous iron dextran

The intravenous use of iron dextran has been recognised by a number of
research clinicians to be a viable therapeutic option in the treatment of iron
deficiency anemias in the Jehovah's Witness patient who steadfastly refuses the
alternative of blood transfusions in order to correct his acquired anemia. The
use of intravenous Imferon and Folic Acid coupled with intramuscular injections
of B-12 and nandrelone decanoate, and at times, when indicated, intravenous
hyperalimentation has become a life saving reality. It is our purpose in this
report to outline our clinical results with Jehovah's Witness patients who
received intravenous iron dextran in the past nine years.

Eight hundred and forty one Jehovah's Witness patients ranging in age from 11
years to 89 years received intravenous iron dextran, and Folic Acid therapy, as
well as intramuscular injections of B-12 and Deca-Durobolin, for the purpose of
correcting iron deficiency anemia. This study began in 1974 and, to date, is
continuing as part of an ongoing treatment modality for anemic Jehovah's Witness
patients. The amount of Imferon needed was calculated from the formula - total
dose of iron to be administrated = 3 x weight in pounds of the patient x the
deficit in hemoglobin. Another formula which can be used is:

$$0.3 \times \text{body weight} \times \frac{(100 - Hb \times 100)}{14.8} = \text{mgm iron}$$

One half cc of Imferon was given as an intravenous test dose over a five minute
period during which vital signs were carefully monitored; when no adverse
reactions were noted, the remaining amount of Imferon was given over a two to
three hour period diluted in 1,000 cc of normal saline; the maximum amount given
to a single patient was 105 ml.

Six to eight mg of Folic acid was given intravenously every day until either
the patient left the hospital, or intravenous therapy was no longer needed.
Intramuscular injection of a single dose of 300 mg of Deca-Durobolin was given as
a single treatment, 2 cc of Vitamin B-12 were likewise given intramuscularly
initially and repeated four times every other day on each patient. Intravenous

hyperalimentation was administered when judged appropriate. Folic acid assays showed that the measured blood levels in those patients had been generally low. CBS and reticulocyte counts were obtained daily. The most frequent causes of anemia were gastrointestinal and vaginal bleeding, malignancy, surgery, and trauma. The hemoglobin levels of the patients included in this study ranged from 1.6 gms to 9.2 gms per 100 ml of blood. 208 patients had a hemoglobin below 5 gms.

No appreciable change in the hemoglobin concentration was noted for the first twenty-four hours, after which the hemoglobin concentration rose at an average rate of 0.41 gms ($\pm$ 0,3 SD) per day. Younger patients with hemoglobin levels below 5 gms per 100 ml and who were suffering from malignant diseases showed the greatest improvement in this series, while older, debilitated patients with advanced cancer and renal problems showed the least improvement. In some cases the debilitated group of patients increased their hemoglobn production following supplementary addition of hyperalimentation - standard total parenteral nutrition providing 1 calorie per cc.

Patients with known severe drug allergies, severe asthma, advanced rheumatoid arthritis, and other auto-immune diseases were excluded from this study. Twelve patients developed mild and transient reactions including superficial phlebitis, fever (less than 100°F), rash and myalgia. No respiratory complications were noted and no anaphylactoid reactions were seen. There was no mortality. In 33 of these patients intra-operative liver biopsies were performed at various intervals following the iron therapy as part of a follow-up; these liver biopsies were not performed as a separate scheduled procedure, but incidently performed during elective or emergency operations subsequently performed on these patients. No liver dysfunction or hemosiderosis was noted in any of these patients.

Intravenous administration of Imferon is the most effective way of restoring depleted iron stores in man. The intramuscular route is painful and the product stains the skin, binds to muscle, and has been shown to cause fibromyosits, as well as soft tissue sarcomas at the site of the injections. Iron is absorbed

more slowly with much less uniformity after intramuscular administration when compared with the intravenous option. The oral administration of iron is poorly tolerated by the severely anemic and debilitated patient and especially in those suffering from various degrees of ileus, intestinal obstruction, colitis, malabsorption syndromes, gastritis, peptic ulcers, and inflammatory bowel diseases. The dark colour of the stool often alarms the Jehovah's Witness patient needlessly since they tend to confuse this alteration in color with melena. In 1973, the Food and Drug Administration approved the use of intravenous Imferon, and thus, opened the door for the option of using total dose infusion as an alternative to blood transfusons in the Jehovah's Witness patient.

Adverse reports in the literature relating to the intravenous total dose infusion have been sporadically reported. They included reports of arthralgia, myalgia, fever, rash, thrombophlebitis, pulmonary emboli, headaches, asthma, wheezing, and occasionally respiratory arrests. These reports have heightened the level of concern among physicians and limited the use of this therapy in the U.S.A. Our experience has demonstrated that, by excluding the patients with known severe drug related allergies, asthma, rheumatoid arthritis and other auto-immune diseases from this treatment plan, this modality becomes an extremely reasonable approach for rapidly correcting anemia without the use of blood transfusions

Hemotherapy has been reported to cause hepatitis, febrile reaction, genetic sensitization, disseminated intravascular coagulopathy, microemboli, and has been implicated in the transmission of malaria and syphilis. This type of therapy carries a greater risk than does the intravenous use of iron dextran. In a collected series of over 2,000 patients receiving Imferon, Wallerstein (1968) showed that only 1 to 2% of the patients developed a reaction to this therapeutic modality.

We feel that the use of normal saline as a diluent to iron dextran has greatly contributed to the reduction of incidents of allergic reactions and phlebitis reported by other investigators using Dextrose and Dextran. Some

physicians have been administrating undiluted Imferon to their patients, though we do not recommend it.

The intravenously administered iron is picked up by the reticuloendothelial system and the liver. The body's capacity to store iron is variable. We have had the opportunity of performing liver biopsies on patients who have received Imferon at various intervals following the treatment and found no evidence of liver dysfunction or hemosiderosis. After administering 3.000 mgs intravenously, Wallerstein (1968) discovered that serum iron decreased linearly at a rate of 525 micrograms per hour. Five weeks following administration, serum iron levels were recorded at 40 micrograms per 100 ml.

The addition of Folic Acid, Vitamin B-12, Deca-Durobolin and hyperalimentation when appropriate, has greatly improved the rate of hemoglobin production in the severely anemic patient and certainly provides the necessary stimuli, as well as the building blocks for an accelerated hematopoietic response.

We can only hope that further intensive clinical and laboratory research will add to the scientific data available to date, as well as improve on the safety aspect of total dose infusion of Imferon, to make it a significant entity in the treatment of iron deficiency anemia. We are also anxiously waiting to see the data on work performed by some investigators on the role of erythropoietin in raising hemoglobin levels in anemic patients. We certainly hope that this substance can be incorporated in the future to the treatment plan which we have described above and that this will improve on our results.

CHAPTER V

FLUOROCARBONS

V-i Introduction

V-i-1 Historical Evolution of the use of perfluorochemicals as blood substitutes

The idea that perfluorocompounds may act as oxygen carriers to sustain life
may have started from the communication of Kylstra (1962) of 'mice as fish', when
he showed that mice could be kept alive when immersed in hyperbaric solutions of
oxygen in aqueous saline solutions. Howlett (1965) used perfluorocompounds as
blood oxygenators, while Clark and Gollan (1966) demonstrated the high oxygen
solubility of perfluorochemicals (PFCs) by submerging mice in its liquid for
extended periods. Their animals were able to obtain sufficient oxygen by
breathing the liquid and, upon removal, showed no apparent ill effects from the
experience. The authors also showed that breathing such liquids can protect mice
from the effects of rapid decompression and he suggested that the liquids would
be useful for such applications as escape from submarines and deep-sea diving.

As also shown by Clark and Gollan, oxygen is highly soluble in liquid PFCs.
Whereas normal saline or blood plasma dissolves about 3 percent oxygen (by
volume) and whole blood with a normal haemoglobin concentration contains about 20
volume percent, pure PFCs dissolve 40 percent or more. Carbon dioxide is at least
twice as soluble. The solubility of oxygen in water, some nonpolar liquids and
PFCs are shown in Tables VI and VII.

Clark and Gollan (1966) were the first to attempt to use perfluorochemicals,
instead of blood, to supply an organ with oxygen when they showed that an
isolated heart of a rat would continue to contract vigorously when perfused with
a perfluorocompound saturated with oxygen.

Preliminary experiments with emulsions of PFCs have shown much promise.
Sloviter and Kamimoto (1967) have shown, for example, that isolated rat brains

Table VI: Solubility of oxygen and carbon dioxide in PFCs

Compound	Temp. °C	Solubility O2 (ml/100ml)*	Solubility CO2 (ml/100ml)*	N2 (ml/100ml)*
Perfluorotetrahydrofuran	25	12.6 (air)	-	27.9 (air)
	37	11.7 (air)	-	26.7 (air)
	25	48.8	192.0	33.4
	37	48.5	160.0	34.0
Perfluorotributylamine (FC-43)	25	10.3 (air)	-	22.8 (air)
	37	10.4 (air)	-	21.6 (air)
	25	38.9	152.0	28.4
	37	40.3	142.0	28.6

Compound	Temp. °C	(Vol %)**	(Vol %)**	
Perfluorotetrahydrofuran	37	58	147	
Perfluorotributylamine	37	41	108	
Perfluorooctane (C8F18)	37	48	180	
Freon E3	37	56	43	
Freon E4	37	36	77	
Perfluorodecalin (FDC)	37	45	134	
Perfluoromethyldecalin	37	42	126	

(Geyer 1975)

*Solubility in liquid PFCs
**Solubility in PFCs as dispersion stabilized with Pluronic F-68

Table VII: Solubility of oxygen in water, silicone, and organic liquids

Liquid	Solubility of Oxygen* (ml/100 ml)
Acetone	28.0
Benzene	22.5
Carbon Tetrachloride	30.3
Ethyl Alcohol	24.2
Ethyl Ether	44.7
Silicone (20 cs)	18.3
Water	2.9

*Values for 25°C   (Geyer-1975)

perfused with such emulsions retain their activity as well as, or better than they do when perfused with a suspension of erythrocytes. They obtained similar results using the emulsions to maintain normal function in isolated canine kidneys, and have also shown that a substantial portion of the blood of mice and frogs can be replaced by such an emulsion with no apparent ill effects. It was demonstrated that mice, whose blood contained 10 to 20 percent of emulsified Fx-80, could survive for a considerably longer time than controls in an atmosphere containing 4% carbon monoxide.

Geyer et al. (1968) have successfully replaced all of the blood of rats with a PFC emulsion. These animals showed no apparent ill effects from infusion of the blood substitute and immediately began producing erythrocytes and blood proteins. By the time most of the PFC had been cleared from circulation (generally within about a week) the animals had generated nearly all their erythrocytes. Moreover, they had a normal life-span after the replacement. This success, depended on the development of the proper flow characteristics of the emulsion, particularly a reduction in its viscosity, and was the result of five years' work in refining the preparations.

Intravenously injected PFCs can be lethal because they are immiscible with blood and can thus produce embolic phenomena. This problem is overcome by dispersing the PFC into very small particles with the aid of a surfactant. In 1968, Geyer made the fortuitous discovery that members of a family of poly-oxyethylene-polyoxypropylene polymers called Pluronics not only emulsify the organic phase, but also serve as plasma expanders to reproduce the oncotic pressure normally provided by blood proteins. A typical preparation, then, would contain about 15 to 30 percent PFC by weight and 2.5 to 10 percent surfactant in an aqueous solution with an ionic composition resembling that of blood.

Clark (1970) has replaced as much as 90% of the blood of dogs with these emulsions, and has observed no ill effects; some of these dogs were kept alive longer than 4 years after the replacement. Using an oxygen electrode implanted in the brain of these dogs, he has shown that the partial pressure of oxygen in

the bloodstream is at least three times as high under conditions of 90% replacement as it is in control animals. The pressure is also well above that at which the remaining hemoglobin releases oxygen, indicating that all oxygen transport is provided by the emulsion.

The emulsifying agents most used in preparing PFC dispersions have been egg and soybean phospholipids, bovine albumin and especially Pluronic F-68 as mentioned above. The last has played, and continues to play, a crucial role in the field of PFC artificial blood as Geyer (1975) emphasizes in his excellent review. The Pluronic polyols are nontoxic at low concentrations. For a typical Pluronic, the LD50 is more than 10 grams per kilogram of bodyweight and, unlike all ionic and many non-ionic surfactants does not cause hemolysis of erythrocytes.

Fluronic F-68, which has a mean molecular weight of 8,350 is a non-ionic surfactant and detergent. It has been used as an emulsifying, dispersing, wetting and defoaming · agent. Recent clinical and experimental studies have demonstrated that Pluronic F-68 may alleviate some of the adverse effects of extracorporeal circulation. Pluronic F-68, when added to the circulating blood in a final concentration of 0.6 mg/ml, has been reported to reduce fat embolization (Adams et al. 1959; Danielson et al. 1970; Miyauchi et al. 1966; Wright et al. 1963), hemolysis (Miyauchi et al. 1966; Paton et al. 1968; Sloviter and Kamimoto 1967), and sludging (Geyer 1973; Grover et al. 1969) as well as to lower viscosity without changing the hematocrit. These investigators have accepted the use of Pluronic F-68 as an additive for extracorporeal circulation and to allow it in the whole circulation of humans.

It has been shown that perfluorotributylamine (FC-43), emulsified with Pluronic F-68, is quite stable and endures repeated circulation through a hollow-fiber dialyzer and heart-lung machine with bubbling oxygen. This suggests the possibility of using it for continuous perfusion of the isolated kidney. Most investigators, who have used Pluronic F-68 in PFC artificial blood formulations, have not recorded any ill effects from this agent (Geyer 1975; Yokoyama et al.

1975; Clark et al. 1975; Rosenblum 1975; Geyer 1970). It is known that Pluronic F-68 precipitates plasma protein in vitro, and in vivo, at a concentration of 20 mg/ml or more (Rose 1966). This polyol is, however, very rapidly excreted from the circulation via the urinary path (90% or more elimination in 3 hours after intravenous injection of 2g/kg body weight of rabbit, (Okamoto 1975))and is not retained in body tissues. In addition, the in vivo precipitation of plasma protein does not occur at 38°C when the concentration of Pluronic F-68 is 8% or lower - this corresponds to an intravenous injection of 3 gm/kg body weight. Geyer (1975) opines that it would seem unwise to eliminate this useful compound until adverse results are observed.

Pluronic F-68 is not capable of emulsifying all types of PFC compounds. For example, Freons E1 and E2 can be emulsified into fine form, but coarse particles occur within a short time and it has not been possible to prepare absolutely stable emulsions of perfluorodecalin (FDC) with Pluronic F-68. A number of PFCs have been tested for emulsion stability as summarized in Table VIII by Geyer (1975).

Because of the excellent stability and ready availability of the emulsifiers, FC-43/Pluronic F-68 emulsion was selected as the most suitable for use in animal experiments (Geyer 1970; Geyer 1975; Yokoyama et al. 1975; Clark et al. 1975; Rosenblum 1975). In 1973, Geyer showed that his 'bloodless rats', whose blood has been totally replaced by FC-47, survived the replacement and in 10 days the plasma protein and hematocrit levels were back to normal. The animals continued to grow and develop normally. It should to be noted, however, that FC-43 in the emulsion is retained in the liver, spleen and other organ tissues for long periods of time.

Apart from Pluronic F-68, purified yolk phospholipids are known to be safe emulsifying agents, that are, moreover, easily metabolized in the body. Soybean-oil emulsified with yolk phospholipids (Intralipid) was developed by Wretland (1972) and has been widely used since 1968 for intravenous nutrition in over a million cases with no confirmed report of untoward reactions. If this substance

Table VIII: Some PFCs used in artificial blood and stability of their emulsions stabilized with Pluronic F-68

Compounds	Emulsion Stability
Perfluorotributylamine (FC-43)	Excellent
Perfluorodecalin (FDC)	Fair
Perfluromethyldecalin (FMD)	Fair
Perfluorobutylterahydrofuran (FC-75)	Fair
Perfluoroadamantane	Fair
Perfluorodimethyladamantane	Excellent
Perfluorodecane	Fair
Perfluorodi-tert-butylether	Good
Freon E3	Excellent
Freon E4	Excellent
Freon E5	Excellent

(Yokoyama et al. 1975; Clark et al. 1975; Clark 1974; Green Cross Technical Information 1975).

(Geyer 1975)

is used for emulsifying PFCs, there should be no objection to its use for systemic infusion. Yolk phospholipids alone, are weak surfactants, and are not capable of emulsifying all kinds of PFCs. For example, when FDC is mechanically emulsified with this agent, it tends to agglomerate and form coarse particles within a few days. Yokoyama (1975) found that the FCD/yolk phospholipids emulsion becomes stable when a small amount of some fatty acid and glycerol is added.

Some investigators have been unable to duplicate the life-saving effect reported by the pioneers, but it now seems likely that this is a result of variability of the preparations, particularly particle size distribution in the emulsions.

Once Fluosol-DA 20% had been prepared as a blood substitute, clinical studies in seven traumatically decerebrate patients were carried out. These subjects were given infusions of the emulsion at dose level ranging from 200 to 1500 ml. No adverse effects were discovered in these patients. In 1979, twelve healthy Japanese volunteers received infusions of 20 to 500 ml without ill effects. To date over 200 infusions of Fluosol-DA 20% have been administered in Japan. In 1980, clinical trials on the basis of emergency treatment began in the U.S.A. on Jehovah's Witness patients. The patient with the lowest hemoglobin level (1.6 gm%) to receive the emulsion, and survive the surgical procedure, was reported by Tremper and Lapin in 1981.

V-i-2 PATHOPHYSIOLOGY OF FLUOSOL-DA 20%

The main ingredients of Fluosol-DA were chosen on the basis of relatively rapid elimination from tissues. A further consideration was the feasibility of preparing stable emulsions. The half-lives of FDC and FTPA, calculated from the expiratory excretion rate, are 7 and 65 days respectively. The calculated

Table IX: Comparison of tissue retention of FDC and FTPA in rats following
intravenous injection of emulsion is each substance

Tissues	Time after injection	% of given dose	
		FDC	FTPA
Liver	1 week	8.50	10.40
	2 weeks	0.50	4.60
	4 weeks	0.09	2.30
Spleen	1 week	4.00	6.90
	2 weeks	0.40	5.80
	4 weeks	0.20	1.20
Kidney	1 week	0.04	0.03
	2 weeks	n.d.	tr
	4 weeks	n.d.	n.d.
Lung	1 week	tr.	0.01
	2 weeks	n.d.	tr
	4 weeks	n.d.	n.d.

tr: trace; less that 10mg/g wet tissue   (Green Cross Manual)
n.d. not detected; less than 1 mg/g wet tissue

overall half-life of Fluosol-DA 20% is 8.9 days (Yokoyama et al. 1975).

Researchers have been concerned with organ retention of fluorocarbons and Table IX shows the comparative data of retention of FDC and FTPA in the main organs of rats following intravenous injection of emulsions of each substance. Each of the PFC were emulsified to an identical particle size of about 0.1 micron diameter (Yokoyama et al 1974). In the case of FDC, yolk phospholipids were used as the emulsifying agent and for FTPA, Pluronic F-68 was used. The concentration of PFCs in organs was determined 4 weeks after injection of the substances at a dose of 4 g/kg body weight. Quantitative determination of PFCs throughout this study was made by gas chromatographic means.

As seen in Table IX, both PFCs were taken up in the liver and the spleen in the majority of animals and the maximum deposition in these organs occurred at 4 days after injection. Significant differences were found in the elimination rate between the PFC emulsions. The concentration of FDC retained in the liver at 4 weeks after injection was far less that 0.1% of the given dose, while that of FTPA was about 3%.

PFCs are mainly excreted through the lungs and the elimination is exponential. The retained amounts of the substances in the body were calculated by summing the total amounts of expiratory compounds excreted. Excretion has also been found via the skin and the biliary tract, but the amounts excreted are very small in comparison to those leaving via the lungs. The size of the particles is apparently important in relation to the retention of PFCs, the larger particles being more rapidly removed from the blood stream than the smaller ones. In rabbits, the half life of a fine PFC emulsion with an average particle size of 0.1 micron, is about 85 hours, while that of a coarse emulsion, with average particle diameter of 0.25 micron, is about 30 hours. The particle size significantly influenced the deposition rate of particles in the reticulo-endothelial system of the liver and spleen, and was also closely related to the toxicity of the emulsion.

A major problem of PFC emulsions as artificial blood substitutes has been

that the compounds are retained in the tissues of animals for long periods of time, especially in the liver and spleen. In order to solve this problem, 100 or more mixtures of PFCs have been examined by many workers. Sixteen different PFC substances were examined by Naito et al. (1978). They found that compounds which have a high vapor pressure (exceeding 20 mm mercury) caused lung emphysema and are highly toxic.

The excretion rate is roughly proportional to the vapor pressure of each substance. The half-life of Perfluorodecalin(FDC), the most rapidly excreted, is 7 days and the amount retained in the body at 50 days after injection was less than 1%, while the half-life of FC43 was about 900 days. FTPA half-life is 64.7 days.

FDC has been found to be the best of the available PFCs with respect to the rate of excretion, but it has been difficult to prepare a fine and stable emulsion of this substance. In order to improve the performance of the perfluorodecalin emulsion, a comprehensive screening programme was enacted to find a suitable emulsion as an artificial red cell substitute, stable both in vivo and in vitro. After various trials, the combined use of FDC and FTPA was found to produce a fine and stable emulsion. FTPA was selected as one of the components of the blood substitute because of its low toxicity and relatively rapid elimination from the body. The half-life in rats is about 65 days. It is longer than that of FDC, but still shorter than that of the other perfluoro-alkylamine compounds. A mixture of 7 parts decalin and 3 parts of propylamine was selected as the best formulation.

The perfluorochemical emulsion, which was named Fluosol-DA, is an emulsion consisting of 20% perfluorochemical, that is 7 parts of FDC and 3 parts of FTPA, Fluronic-F68 and yolk phospholipids as emulsifiers, and glycerol as a stabilizer. To furnish the preparation with physiological osmolarity and oncotic pressure, Krebs-Ringer's bicarbonate solution and hydroxyethyl starch (HES) were added.

The volume of oxygen dissolved in Fluosol-DA changes linearly with PO2 according to Henry's law. The uptake and release of oxygen is completely
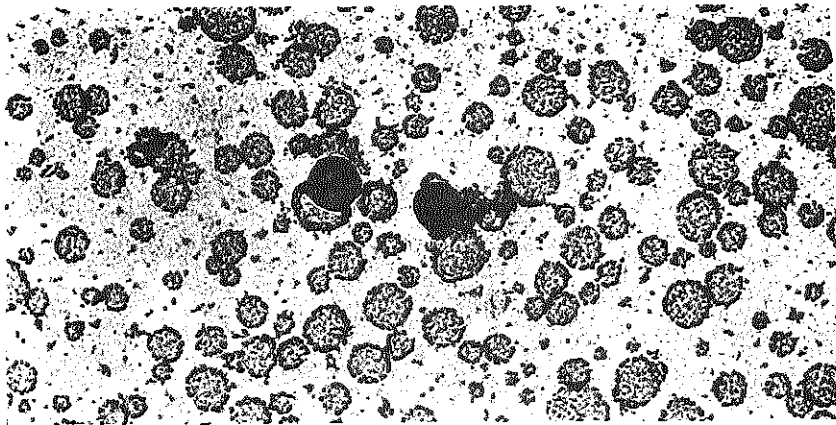
Fig 4 Electron-micrograph of 'Fluosol-DA 20% emulsion
The dark beads in the center are polystyrene latex
particles of 0.1 micron in diameter as the marker.
The particles surrounded by dark dots (phospholipids)
are particles of perfluorochemical substance.

Table X: Distribution of FDC and FTPA in tissues of dogs exchange-transfused with Fluosol-DA (Hct: 4-5).

Tissues	PFC concentration (mg/g wet tissue)					
	1 month		2 months		6 months	
	FDC	FTPA	FDC	FTPA	FDC	FTPA
Brain	0	0	0	0	0	0
Heart	0	0	0	0	0	0
Lung	0.11	0.63	tr	tr	0	0
Liver	18.97	29.43	tr	7.67	0	tr
Spleen	48.07	60.65	tr	5.38	0	0.99
Kidneys	0.51	1.03	tr	tr	0	0
Adrenals	4.30	5.62	tr	tr	0	0
Pancreas	6.88	8.81	tr	tr	0	0
Small Intestine	0.63	0.79	0	tr	0	0
Large Intestine	tr	0.70	0	0	0	0
Stomach	0	0	0	0	0	0
Testicle	0	0	0	0	0	0
Muscle	0	0	0	0	0	0
Femoral Marrow	4.05	4.92	tr	1.33	0	tr
Adipose Tissue	0.74	2.11	0	0	0	0
Bile (mg/ml)	55.80	102.90	21.90	38.70	0	13.20

Yokoyama et al. 1977

reversible like hemoglobin and the rate is twice as fast as hemoglobin. Fluosol-DA can deliver an amount of oxygen equivalent to blood with a hematocrit of 30 to 40% when tissue PO2 moves from 550 mm mercury to 50 mm mercury. However, Fluosol-DA in the circulation can only transport sufficient oxygen from the lung to peripheral tissues when the inspired pO2 is high enough.

The particle size distribution of the emulsion, which was determined by the centrifugal sedimentation method, is in a narrow range and 90% or more of the particles by weight were smaller than 0.2 micron in diameter. The particle size of the emulsion has also been confirmed by electron microscopy as shown in Figure 4. The dark beads in the center of this picture are polystyrene plates, 0.1 micron in diameter, which were mixed in the emulsion as a control. The particles of Fluosol-DA are surrounded with a phospholipid layer which is 40 A thick. The size distribution of particles was found to be closely correlated with that obtained by the centrifugal sedimentation method.

The retention of Fluosol-DA particles in the circulation is essential because the oxygen carrying capacity of Fluosol-DA is dependent on the concentration of PFC in the circulation. Rats and dogs had about 90% of their own blood replaced with Fluosol-DA and the elimination rate of PFC from the circulating blood was examined. In both species, the PFC was eliminated from the circulation according to the first order process, and the half-life of PFC in the circulation was calculated to be 14 hours in rats and 25 hours in dogs. In humans, it is not yet known.

It has been well known that PFCs accumulate in some organs, especially in the liver and spleen, after leaving the circulation, and then are gradually excreted, unmetabolised, through the lungs. Table X shows the distribution and elimination of FDC and FTPA in dogs hemodiluted with Fluosol-DA until the hematocrit reached 5%. The net dose given was about 15 grams per kilogram body weight and this is equivalent to around 5,000 ml of the emulsion per human adult. The concentration of both PFCs in the tissues of dogs was highest in the spleen and a level of 50 to 60 milligrams per gram of tissue being was one month after administration. The

concentration in the liver was about half of that in the spleen. Smaller amounts of PFCs were also found in other organs after one month, but no PFC's were detected in the brain, heart, or testes. Two months after hemodilution, only trace amounts of FDC were found, while after six months FTPA was found at concentrations of about 1 milligram per gram of wet tissue.

Rats were exchange transfused with Fluosol-DA under pure oxygen respiration until the hematocrit reached 1% and 4% corresponding to 98% and 92% replacement of their own blood, respectively. As a control, 3% hydroxyethyl starch (HES) solution was used. Bleeding from the carotid artery and replacement with an infusion of Fluosol-DA through the tail vein was repeated until the desired hematocrit was obtained. Fluosol-DA significantly prolonged the survival time of both groups of exchange transfused rats. Another study of distribution and elimination of FDC and FTPA, performed in dogs exchange transfused with Fluosol-DA until hematocrit levels fell below 5%, showed that the concentrations of FDC and FTPA in tissues at 4 weeks after transfusion were highest in the spleen, showing at levels of 50 to 60 mg/g wet tissues. The concentrations of both PFCs in the liver were about a half of those in the spleen. Small amounts of both PFCs were also found in the lung, kidneys, adrenal, pancreas, intestine, bone marrow, adipose tissue and bile at 4 weeks, but no PFCs were detected in the brain, heart, or testes. FDC was eliminated faster from the tissues than was FTPA. At 2 months after hemodilution none, or only trace amounts of FDC were found, while about 1 mg/g wet tissues of FTPA was found in the spleen while traces were still retained in the liver and bone marrow even after 6 months. Net doses of PFC given were equal to 15 g/kg.

Similar results were also found in monkeys hemodiluted with Fluosol-DA until hematocrit reached 1%. At 2 and 4 months after hemodilution the monkeys were sacrificed and the concentration of PFCs in the tissues was determined. At 2 months the concentration of both PFCs were found to be higher in the liver, spleen and bone marrow as compared to other tissues and no significant difference of the concentration in those tissues was observed between FDC and FTPA.
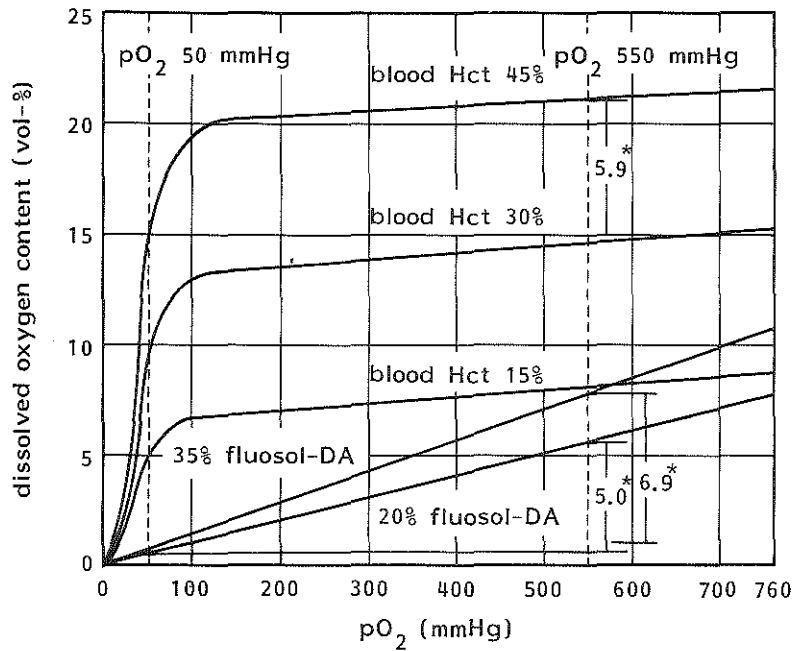
Fig 5 O_2-dissociation curves of "fluosol-DA" and whole blood

* This shows the oxygen content (vol-%) which can be released from "fluosol-DA" and whole blood (Hct 45%) with pO_2 drop from 550 to 50 mmHg.

However, the concentrations of FDC so localized in these sites rapidly decreased and no FDC was detected in these organs at 4 months after hemodilution, while approximately 2 mg/g of FTPA was still found only in the liver and spleen. The net dose of PFC given was 25 g/kg.

The rate of recovery of the blood components which are lost by the exchange transfusion with PFC emulsion is very important. It was shown that in rats with 92% of their blood replaced with Fluosol-DA, plasma protein levels and white blood cell counts recovered completely within 3 days. The recovery of the hematocrit was somewhat delayed but it returned to the normal range within 2 weeks. The respiratory function of the lung was well maintained during and after exchange-transfusions and no abnormalities in either kidney or liver function were found one week after the administration of Fluosol.

The amounts of oxygen that are carried by fluosol depends on the pO2 of the solution. Unlike haemoglobin, which has the well known s-shaped dissociation curve, the uptake of oxygen of fluosol is directly proportional to pO2. These relationships are illustrated in Fig 5. It can be seen that the amount of oxygen released in the tissues (at a pO2 of 50 mm Hg) by a solution of fluosol saturated with oxygen at a partial pressure of approximately 500 mm Hg may in some cases be the same or even more than blood.

The oxygen carrying capacity of Fluosol-DA was demonstrated in experiments using large animals such as rabbits, dogs, and monkeys. Occasionally, slight histological changes were observed in the pulmonary alveolar septa in the early period following transfusion but edema was rarely found in the lung. These changes were completely abolished within 6 days. The monkeys hemodiluted with Fluosol-DA remained in good health with no abnormal behaviour one year after the exchange (Gould 1982).

Organ functions, which were temporarily damaged by the severe hemodilution, returned to normal levels within two weeks after hemodilution. At two days after infusion, significant changes were found by optical microscopy only in the liver and spleen. Kupffer cells in the liver were enlarged and proliferated, often

gathered together with fairly abundant, coarsely vacuolater or 'foamy' cytoplasm. Liver cells were not significantly affected but occasionally the cytoplasm were finely granulated or coarsely vacuolated. No necrotic changes occurred. In the spleen, reticular cells of the red pulp were swollen with coarsely vacuolated or 'foamy' cytoplasm. Sometimes, the red pulp was filled with the 'foam' cells. The lymphoid follicles of the spleen were not significantly changed. These histological changes in the liver and spleen were maximal during the first 1 to 2 weeks after transfusion and then gradually returned to normal. The cytoplasmic changes in both organs had virtually disappeared 4 months after infusion and no fibrosis was present.

Electron-microscopic examination revealed the details of the histological changes caused by infusion of Fluosol-DA in the hematocytes and reticuloendothelial cells (Naito and Yokoyama, 1978). Electron-microscopy of the liver at 2 days after a single injection of Fluosol-DA demonstrated the reticuloendothelial cells filled with clusters of vacuoles. Hepatocytes showed some vesicles which contain small vacuoles surrounded by a membrane. However, these vacuoles were commonly isolated from organelles with electron dense membranes, so that substantial changes were not recognised in endoplasmic reticulum, mitochondria and the Golgi's apparatus. The vacuoles found on electron-micrographs have been interpreted as being PFC particles because the amounts seem to be in proportion to the amount of PFC retained in the tissues. At 4 months after infusion, no PFC particles in the hepatocytes were observed; the vacuoles in some reticuloendothelial cells were still retained, but markedly decreased in number as compared with those at early stages after infusion.

Histopathological studies in rats given 40 ml/kg body weight revealed mainly 'foamy' changes in the liver and spleen at 2 weeks but disappeared at 4 months (Naito and Yokoyama, 1978). In monkeys, histopathological changes were noted after Fluosol-DA in a dose of 25 g of PFC/kg bodyweight (Ohyanagi et al. 1977). The light and electron microscopic findings of the liver showed that PFC particles were intensively taken up by the Kupffer cells, but hardly at all by

the endothelium of the sinuses or hepatocytes. PFC particles diminished in their amount with the lapse of time after the infusion of PFC emulsions. No abnormalities of the organellae were observed in the hepatocytes.

The glomeruli and proximal tubules of the renal cortex were histologically normal both at 2 and 4 months after infusion. On the other hand, some pathological findings, such as vacuolar or atrophic degeneration with inter-stitial cell proliferation, were recognised in some parts of the distal tubules of the medulla. As the tubules are one of the most sensitive organs with respect to hypoxia, these findings would seem to indicate repair processes following mild localized tubular necrosis occurring during exchange transfusion. Evidence of edema was noted in the lungs which disappeared after 2 months.

In all of the laboratory experimentations with rats, dogs, and monkeys, no evidence of carcinogenicity were noted (Naito and Yokoyama, 1978).

Our experience with humans revealed histopathological findings very similar to that of the findings in rats and monkeys. Liver sections in the early stages after infusion with Fluosol-DA have revealed enlargement, vacuolization and increase in size of the Kupffer cells lining the sinusoids. The cytoplasmic vacuolization varies from coarse to fine. The hepatocytes were not significantly affected nor was evidence of necrosis observed. Splenic sections have demon-strated early sinus histiocytosis with cytoplasmic vacuolization - a feature which has been observed in experimental animal models.

Lung sections have revealed a variety of non-specific changes in the early stages such as pulmonary edema, vacuolated macrophages within alveolar spaces (heart failure cells) and in several instances, the presence of a hyaline mem-brane lining the luminal surface of the alveolar walls. Renal tissue alterations have not been observed to any significant degree.

We noted elevations of SGOT, SGPT, and alkaline phosphatase immediately after the infusion of Fluosol-DA 20%. The rise of the liver enzymes correlated with the amount of emulsion given. No changes were noted in the blood chemistry. Marked increase in the reticulocyte count were observed following the infusion.

Fluorocrit levels increased proportionately to the amount of PFC given. No evidence of carcinogenicity was observed in any of our patients 2 years after infusion.

We have not used Fluosol-DA 20% on patients with:

a. pulmonary insufficiency (A.R.D.S.)

b. liver dysfunctions

c. renal insufficiency

d. allergic reaction

e. positive Coombs test

f. coagulation defect

Our experience, and that of the Japanese investigators, has demonstrated the safety and feasibility of using PFC as a blood substitute. Although Fluosol-DA can never totally replace all of the functions that blood performs, it can be extremely useful in situations where blood is not available, or in patients who refuse blood transfusions on religious objections.

V-ii   The Experimental Use of Fluorocarbons

Fluorocarbon Mediated Changes in Oxygen Supply in the Ischemically Hypoxic Myocardium - Preliminary Report

Introduction

Cellular oxygen supply is dependent on: first, pulmonary gas exchange; second, oxygen transport capacity of the blood; third, capillary perfusion; fourth, oxygen diffusion through the capillary wall, the intercellular space and across the cell membrane.

If adequate pulmonary gas exchange is maintained, and assuming no change in oxygen diffusion characteristics, oxygen delivery to the tissue depends furthermore on oxygen transport capacity of capillary perfusate, tissue perfusion and distribution of the perfusate through the arteriolar-capillary network.

The effects of occlusion of a supplying artery can be partially compensated for by collateral capillary perfusion resulting in a central totally ischemic area, surrounded by an area with partial collateral perfusion inside an area of active hyper-perfusion (i.e. Occlusion of a branch of the left coronary artery; Reeves et al. 1978).

Collateral perfusion into the border areas of an infarcted region is not, however, sufficient. The main problem seems to be the decrease of the perfusion pressure gradient along the capillary net because of increased length of the capillary pathway to be perfused. Hence, we postulated that blood viscosity should be considered to be a major factor determining flow ratio in collaterally perfused areas.

In the present preliminary study this hypothesis was examined using micro-electrodes directly implanted into the myocardium and we tried to determine to what extent increase of blood fluidity, produced by hemodilution, would increase

the collateral oxygenation of the ischemic area.

In a second study, the influence of oxygen carrying low molecular fluorocarbon (Erdmann et al. 1982) added to the dilutate was studied to examine the reoxygenation of collateral perfusion of occluded areas. This was based on the hypothesis that the rather large oxygen carrying erythrocytes can probably not be transported along the elongated and narrow capillary system because of a too slow static pressure gradient.

Materials and Methods

Juvenile female Yorkshire pigs of 25 kg bodyweight were used in this preliminary investigation.

Electrode Systems:

The measurement of myocardial pO2 was accomplished with the use of four steel protected gold microelectrodes (Clark Electromedical Instruments) and a silver/silver chloride reference electrode. The gold microelectrodes, 200 microns in diameter, were embedded in a thin flexible plastic plate $\pm$ 5 cm x 2 cm, which was sewn onto the epicardium. The distance between the electrodes was 1 cm and they protruded 3 mm into the left ventricular wall to ensure contact with the myocardium. When the gold electrodes are negatively polarized, oxygen was reduced, causing a current to flow to replenish the electrons used up in the process. At a voltage of -800mV, this current is directly proportional to the oxygen concentration. To ensure partial pressure measurement, the electrode tips are covered with a plastic membrane, which also prevents protein poisoning and minimizes convection dependency. Because the currents are so small (1-20 namoamperes) measurements must be performed in an isolated Faraday Cage. Before starting the experiment, the electrodes were calibrated in a 37°C saline solution, through which gases of known oxygen partial pressure were bubbled for equilibration. After the experiments the electrodes were again calibrated to

ensure reliability and to estimate any drift that had taken place.

Anaesthesia and Monitoring

Anaesthesia was induced with an intraperitoneal injection of sodium thiopentone (30 mg/kg bodyweight). After intubation with a cuffed endotracheal tube the animals were ventilated with 0.5% fluothane in 100% oxygen using a Minivent ventilator adjusted to maintain the arterial pCO2 at between 35 and 45 mm Hg. Pancuronium bromide was used to maintain muscular relaxation and this was administered intravenously using a Braun Melsungen Perfuser adjusted to administer the drug at a rate of approximately 0.5 mg/kg per hour.

Through an incision in the groin an arterial catheter was introduced into the femoral artery and advanced into the aorta. A venous catheter was introduced into the femoral vein and advanced into the inferior vena cava. A seven french gauge KMA thermodilution catheter was introduced into the other femoral vein and advanced under pressure monitoring into the pulmonary artery. The arterial line was connected to a Gold Statham P23ID pressure transducer and the pulmonary artery line of the Swan Ganz and the central venous pressure line were connected to Gold Statham P23DC transducers. These together with a Millar microtip pressure transducer PC470, which was introduced into the left ventricle via the carotid artery in the neck, were fed into a 12 channel Grass 7D polygraph and recorded on paper using a Grass ink writing oscilligraph.

Using the above instrumentation the following parameters were monitored: systemic and pulmonary artery pressure, central venous pressure, pulmonary capillary wedge pressure, left ventricular pressure, and left ventricular dp/dt. Cardiac output was determined by thermodilution using a KMA thermodilution cardiac output computer model 3500. Arterial blood was withdrawn at regular intervals for blood gas analysis using a Radiometer ABL1 acid base laboratory. Haemoglobin was estimated using a Radiometer OSM2 hemoxymeter. The thorax of the animal was opened using a sternal splitting technique and the pericardium was reflected. The pig was moved into a Siemens electrically isolated Faraday Cage

to minimize noise interference and all lines were led outside via the grill 'windows' to transducers and recording apparatus. The pig lay on a warming mattress through which warm water was pumped by a GRI aquamatic K heater circulator module. The pO2 microelectrodes protruding through the plastic plate, as described above, were sutured onto the epicardium after the electrodes had been placed in position in the expected area of distribution of the chosen branch of the left anterior descending coronary artery (LAD). This was a branch that was constantly observed issuing laterally and to the left from the LAD about 2-3 cm above the apex of the heart. The electrical output from the electrodes was amplified by DC amplifiers inside the Faraday Cage and the resulting signals were fed into Rikadenki electronic recorder model KA60. The experimental arrangement is demonstrated diagramatically in Fig. 6.

After allowing time for stabilization of the preparation of ligature was placed around the chosen branch of the LAD and the vessel was occluded. In one animal no treatment was administered, and after four hours it was sacrificed by ventilating with 100% nitrous oxide - this usually results in total cessation of circulation within five to ten minutes. The heart was removed and examined macroscopically and microscopically for signs of infarct.

In the second animal bleeding was begun after one hour of vascular occlusion. 20 ml of blood per kilogram bodyweight was removed and then immediately replaced with the same volume of a fluorocarbon solution (fluosol - DA 20%) the animal was again sacrificed four hours post-clamping and the heart examined by the pathologist.

In the third animal, dextran 40 (40,000 molecular weight) was used in place of the fluorocarbon solution; again pathological examination of the heart was carried out after the animal had been subjected to an acute hypoxic death. A schematic plan of the experimental protocol is shown in fig. 7. The fluorocarbon and dextran treatments were completed between one and two hours postclamping; the two hours post-clamping values as presented in the results section thus represent values obtained just after the infusion of dextran or fluorocarbons.

Left Intraventricular
Pressure Line

Microelectrodes

CAGE

Amplifiers

FARADAY

Central Venous
Pressure Line
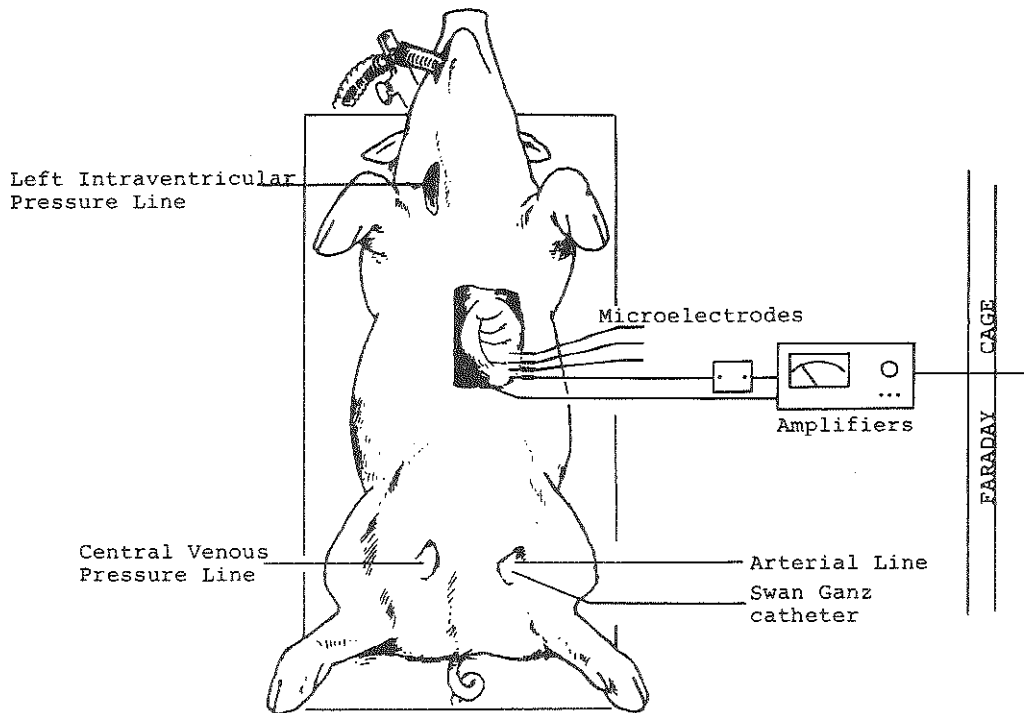
Arterial Line

Swan Ganz
catheter

Fig 6 Schematic diagram of the experimental arrangement - 4 microelectrodes, 200 microns in diameter were inserted in the distribution area of a terminal branch of the LAD.
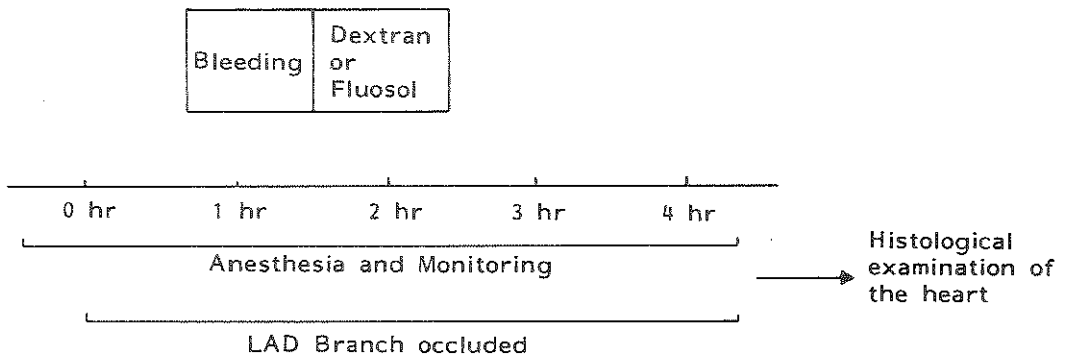
Bleeding	Dextran or Fluosol

0 hr   1 hr   2 hr   3 hr   4 hr

Anesthesia and Monitoring

Histological examination of the heart

LAD Branch occluded

Fig 7 Sequence of experimental procedures

Pathological Examination:

After macroscopic inspection, three slices were cut from each heart, about 0,5 cm thick. Slice 1 was taken from just distal to the point of occlusion of the artery - the anterior left ventricular wall in this specimen represents the direct area of supply of the occluded artery. Slice 2 was about 1 cm above Slice 1, (in the direction of the atrio-ventricular valves) and Slice 3 was approximately 2 cm above Slice 2. The anterior ventricular wall in Slices 2 and 3 lies under the area covered by the electrode bearing plastic plate.

Tissues blocks were taken from any macroscopically abnormal area observed, or if no abnormality was present an 'at random' block was taken from the anterior left ventricular wall. Per heart, two to three tissue blocks were obtained. These blocks were fixed for 24 hours in 10% formalin and then embedded in paraffin wax. Five micron thick sections were taken and stained with the hemotoxolin-azophloxin technique.

Results

Myocardial Oxygenation Changes:

It was impossible to know exactly where the most hypoxic area was likely to be situated following occlusion of the chosen branch of the left anterior descending coronary artery. Therefore, four electrodes, as described above, were placed throughout the area were ischemia was to be expected. After occlusion, pO_2 dropped in those areas where perfusion was decreased while in the unaffected areas it remained at the original level. In the following description we have concentrated on describing the changes in the area which was most ischemically hypoxic. All pO_2 tracings were therefore studied and the most hypoxic area was chosen as being in the region of the electrode demonstrating the greatest percentage fall in pO_2 one hour after ligation of the artery when comparing the values to the preligation values. The readings from that electrode are presented.
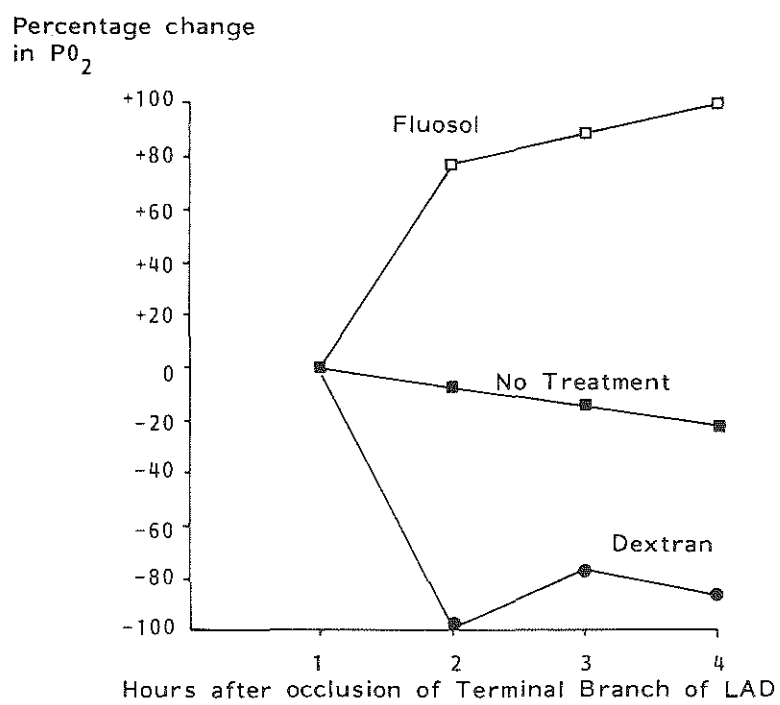
Percentage change
in PO_2

Fig 8 Changes of myocardial pO2 in the experimental groups. Baseline measurements were taken of the microelectrode showing the greatest percentage fall from the preocclusion value.
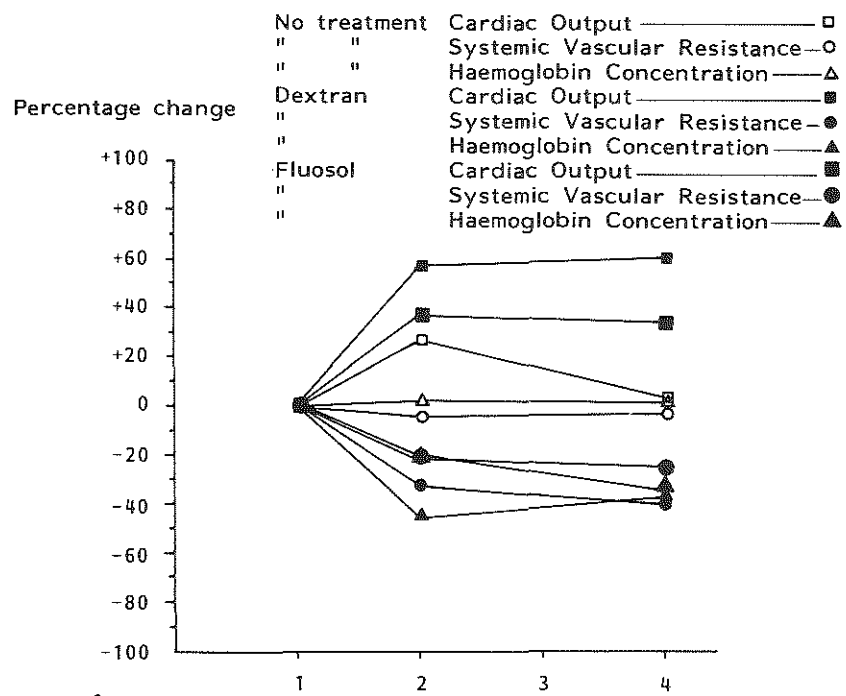

Fig 9 Hours after occlusion of Terminal Branch of LAD

Figure 8 is a graphical representation of the percentage changes in pO2 taking place in the most hypoxic areas in three pigs, whereby the changes are expressed as percentage change from the values one hour after vascular occlusion; i.e. the post-occlusion hypoxic value is taken as the baseline for further changes.

As can be readily seen in the pig that received no treatment following occlusion, there was a steady drift downwards of the myocardial pO2 from the one hour post-occlusion value. Four hours after ligation the value was 21.4% lower than one hour after ligation.

In the case of the pig treated by bleeding 20 cc of blood per kilogram body weight and replacement by the same volume of dextran 40, a dramatic 91.7% fall of pO2 was observed at two hours post-ligation i.e. immediately following infusion of dextran. At four hours this was still decreased 86.1% from the baseline.

In the pig treated by bleeding followed by reinfusion of the same volume of fluorocarbon solution, a marked rise was observed in the myocardial pO2 in the hypoxic area. This amounted to 77.8% at two hours after ligation. After a further two hours there had been a further rise to produce a value of 100% increase above the direct post-clamping value.

Cardiovascular Changes:

Percentage changes in cardiac output, systemic vascular resistance, and haemolgobin concentration are represented graphically in figure 9.

Both fluorocarbon and dextran treated pigs showed rises in cardiac output and falls in vascular resistance after their respective treatments. Changes seen in the dextran pig were more pronounced than those in the fluorocarbon pig - cardiac output in the dextran pig rose by 57.1% and 61.1% at the two and four hour post-clamping respectively while its systemic vascular resistance decreased by 32.6% and 38% over the same period of time. In the case of the fluorocarbon treated pig, cardiac output rises of 36.8% and 34.6% were measured with corresponding 21.2% and 24.6% decreases in systemic vascular resistance.

A greater percentage fall in haemoglobin concentration was observed in the dextran pig as compared to the fluorocarbon treated one - decreases of 45.1% and 36.3% in the former as against 20.8% and 32.1% in the latter.

No significant changes of blood pressure (i.e. perfusion pressure) were observed in any of the animals.

Pathological Changes:

Macroscopically it was ascertained that the chosen branch of the LAD was completely occluded. Four small holes were present over the left and right ventricular wall on each heart representing the sites of insertion of electrodes; in addition holes made during suturing of the plastic electrode plate were visible.

Inspection of the tissue specimens revealed heamorhagic mottling in the anterior left anterior wall in Slice 1 from all hearts. In the no treatment heart, no discolouration was seen in Slices 2 and 3 whereas, in the dextran heart, slight haemorrhagic discolouration was observed in the left anterior ventricular wall in both Slices 2 and 3. The fluorocarbon treated heart showed slight haemorrhagic mottling of the anterior left ventricular wall in Slice 2 but not in Slice 3.

Microscopically, all hearts showed marked epicardial infiltration with polymorphonuclear leucocytes. The site of insertion of the electrodes was clearly indicated by a 'hole' in the myocardium, surrounded by eosinophilically charged myocardial fibres. Eosinophilia of the myocardium was taken, not so much as a sign of ischemia, but more as an indication of mechanical damage.

'Waviness' of the myocardial fibres was used as a 'marker' of ischemic change (Bouchardy and Manjo, 1974). Areas of extensive coherent 'waviness' were demonstrated in the immediate area of supply of the occluded artery (Slice 1) in all hearts. Similar areas of 'waviness' were observed in the anterior left ventricular wall in Slices 1 and 2 in both the no treatment and dextran treated hearts. In contrast, in the fluosol treated heart only localised 'waviness' of a

few myocardial fibres was observed.

Discussion

The hypothesis was studied that decrease in viscosity and hence a decrease in the flow resistance along ateriolar-capillary collateral circulation should increase collateral perfusion of the ischemic areas and therefore increase oxygen supply.

Although dextran decreased flow resistance decisively (as evidenced by decreased systemic vascular resistance) with a corresponding increase of cardiac output and decrease of haemoglobin concentration, oxygenation of the ischemic areas deteriorated more than in the untreated animal.

This leads to the conclusion that, under conditions of ischemic hypoxia, viscosity per se is not the determining factor in tissue oxygenation - even in the presence of increased cardiac output and assumed increased tissue perfusion.

To study whether this was a question of increased perfusion outside the ischemic areas or of inability of oxygen carrying erythrocytes to penetrate the ischemic capillary bed (although erythrocyte-free plasma perfusion was increased), a molecular small volume oxygen carrying substance in the form of the plasma expander fluosol-DA 20% was used for blood replacement. In spite of the fact that this ready-for-use blood substitute did not produce as much apparent changes in viscosity as dextran (less decrease of the systemic peripheral resistance and haemoglobin concentrations) and therefore less increase of cardiac output, (and hence less tissue perfusion), tissue pO_2 was decisively improved in the ischemic area.

Thus the inability of red cells to be forced through an elongated collateral perfusion pathway to supply an area ischemically cut off from the direct blood supply, would appear to be a major contributing factor in determining the ultimate infarct size.

The pathological findings would indicate that fresh myocardial infarction was present in all hearts, however, in the fluorocarbon treated heart the infarcted area was localised and limited in extent to the immediate area of supply of the occluded artery while in the no treatment and dextran treated hearts the infarction extended far beyond this expected area of immediate supply. This would indicate that though fluorocarbon treatment cannot prevent myocardial infarction it can significantly reduce its extent.

The present experiments suggest that low volume oxygen carrying molecules can indeed penetrate collaterally perfused capillary beds to replenish oxygen supply.

This may well indicate a promising approach to future clinical treatment of fresh infarction.

90

V-iii   The Clinical Use of Perfluorocarbons

The Preoperative Treatment of Severely Anemic Patients with a Perfluorochemical
Oxygen Transport Medium Fluosol-DA 20%

This study has been published in the New England Journal of Medicine.

ABBREVIATIONS

Cardiac Index - CI

Left Ventricular Stroke Work Index - LVSWI

Oxygen Delivery - O2 Del

Total body oxygen consumption - VO2

Hematocrit - Hct

Fluorocrit - Fct

Partial pressure of oxygen (arterial) - PaO2

Oxygen content (arterial) - CaO2

Hemoglobin O2 saturation (arterial) - SaO2

Arteriovenous oxygen content difference - avDO2

Hemoglobin - Hb

Perfluorocarbons - PFC

Partial pressure of oxygen (mixed venous) - PvO2

Oxygen content (mixed venous) - CvO2

Hemoglobin O2 saturation (mixed venous) - SvO2

Positive End Expiratory Pressure - PEEP

Transcutaneous partial pressure of O2 - PtcO2

Introduction

In 1965, Leland Clark dramatically demonstrated the oxygen carrying capablity of perfluorochemicals (PFCs) with the survival of mice completely immersed in the liquid. Since then, work has progressed to the production of stable inert emulsions that act as red blood cell substitutes during complete exchange transfusions in animals. After studies with decerebrate human subjects in 1979, adult volunteers were given the PFC emulsion, Fluosol-DA 20% in Japan (Green Cross Corporation, Osaka, Japan). Last year we reported the first comprehensively monitored administration of Fluosol in the preoperative treatment of severe anemia. This uncontrolled, non-blind study of the effects of Fluosol-DA 20% commenced in November 1979, in patients who required emergency medical/surgical treatment, who refused blood or blood products, and for whom no other acceptable medical treatment existed. The following study reports the results of the comprehensive monitoring of seven anemic surgical patients and represents the first clinical trial of PFC red cell substitute in the United States.

The objectives of this study were as follows; first, to evaluate the clinical safety of Fluosol administration - this was with respect to fluid overload and possible adverse reactions; second, to comprehensively monitor hemodynamic and oxygen transport variables before and after Fluosol administration - this was to determine if Fluosol transported the expected volume of oxygen, based on its known oxygen solubility, and to document the possible physiologic responses to the increase in oxygen content after Fluosol administration; third, to determine the reliability of calculated oxygen content determinations versus directly measured oxygen content values obtained in the clinical setting. Since the direct measurement of oxygen content is not available at most hospitals, whereas PaO_2 is standard, we hoped to determine if an estimate of the CaO_2 value based on PaO_2, SaO_2, hemoglobin and fluorocrit could accurately represent the measured CaO_2 value.

Table XI Patients' Clinical Data.

PATIENT NO.	AGE	SEX	BODY WEIGHT	DIAGNOSIS	HEMOGLOBIN	SURGERY *
	yr		kg		g/dl	
6	31	M	48	Ulcerative colitis	1.9	Colectomy and ileostomy
1	40	F	45	Dysfunctional uterine bleeding	3.5	Total abdominal hysterectomy
7	33	F	78	Uterine fibroid bleeding	4.5	Total abdominal hysterectomy
3	28	M	80	Upper-gastrointestinal-tract bleeding	6.6	Suture ligation of gastric ulcers
2	59	F	91	Upper-gastrointestinal-tract bleeding	7.2	Suture ligation of gastric ulcers
4 †	51	M	102	Upper-gastrointestinal-tract bleeding	7.5	Suture ligation and repair of hiatal hernia
5 †	28	M	64	Upper-gastrointestinal-tract bleeding	3.9	None

*Anesthesia was maintained with enflurane, oxygen, and pancuronium.

†The study was terminated after a clinical reaction to a test dose of fluosol.

Materials and Methods

Clinical Subjects:

The patient admisssion criteria was as follows: First, the patients had to be anemic, hemoglobin less than 8 gram %, and in need of surgical treatment if actively bleeding. Second, the patients were without a history of hepatic, renal or pulmonary disease. This was not only because of possible toxic effects, but also to insure that patients would be able to restore their own hemoglobin if Fluosol were able to help them survive the immediate surgical trauma. Also, if a patient were unable to achieve a high PaO_2 value (300 torr), the oxygen carried by Fluosol would be minimal and not warrant the use of Fluosol. Third, the patients refused blood or blood products.

Seven patients were admitted to the study. Their clinical data and mean hemoglobin values are presented in Table XI. The patients ages ranged from 28 to 59 years, with a mean of 35 years, while their mean hemoglobin values ranged from 1.9 to 7.5 gram %, with a group mean of 5.1 gram %. All the patients were actively bleeding when they entered the study and had failed with conservative therapy. Two of the seven patients had symptomatic reactions to a test done with Fluosol and were discontinued from the study. All five patients receiving Fluosol tolerated surgery well, although the most severely anemic patient (mean Hb = 1.9 gram %) died on the fifth postoperative from multiple complications unrelated to Fluosol.

Preparation and physiologic measurements:

Swan Ganz and arterial catheters were placed in each patient. Each data set included systemic arterial, pulmonary artery, wedge (WP) and central venous pressures (CVP), heart rate, central blood temperature, cardiac output, FiO_2, arterial and mixed venous blood gases and blood oxygen contents, hematocrit, fluorocrit (% of perfluorochemical in a blood sample analogous to the hematocrit), and transcutaneous oxygen (Novametrix Medical Systems, Wallingford,

Ct.). Cardiac output was determined by the thermodilution technique and taken in duplicate. Blood gas samples were taken anaerobically and analyzed for gas tensions and pH with either a Radiometer BMS-3, Mark-2, or IL282 blood gas analyzer, and for oxygen content with a LEX-02-CON-TL (Lexington Instruments, Waltham, Mass.). The fluorocrits were determined by centrifugation of blood samples in capillary tubes for 12 minutes at 10,000 rpm instead of at the required speed of 12,000 rpm for 10 minutes. The accuracy of this method was checked against direct gas chromatographic blood analysis.

Derived variables were calculated by standard formulas. A total of 89 data sets were taken for the five patients completing the study, (18 ± 3 data sets per patient). Approximately 2.5 ml of blood were required for each data set. After placement of Swan-Ganz and arterial catheters, three sets of baseline data were taken with the patient breathing room air. (This was not done with the most anemic patient, Hb = 1.9 gram %). This was followed by three sets of data collected with the patient breathing maximal oxygen by mask.

The patient was then given a 0.5 ml test dose of Fluosol, intravenously. If no adverse reactions were noted, the Fluosol infusion was started at 1 ml per minute and gradually increased to a maximum rate of 10 ml per minute. WP was monitored during Fluosol administration and furosemide was given to WP 18 cm water. The total dose of Fluosol given was 20 ml per kilogram of body weight. Data sets were again collected with the patient breathing room air and maximal inspired oxygen by mask. The patients were then taken to surgery where data sets were collected approximately every 15 minutes. The last three patients entered into the study, had complete blood counts taken just before the test dose of Fluosol, and 5 and 10 minutes after the test dose (discussed below).

Results

Preoperative Control Values:

The hemodynamic and oxygen transport data for the five patients are presented

TABLE XII   Hemodynamic and Oxygen Transport Values (n=5)

Variables, Units	Normal Values	Pre Fluosol		After Fluosol	
		Low FiO2	High FiO2	Low FiO2	High FiO2
HR beats/min	68-76	106 $\pm$ 16	102 $\pm$ 13	114 $\pm$ 13	10 $\pm$ 15
MAP mm/Hg	85-95	86 $\pm$ 10	87 $\pm$ 7	89 $\pm$ 15	91 $\pm$ 20
WP mm/Hg	3-13	5.4 $\pm$ 1.0	5.1 $\pm$ 1.0	14 $\pm$ 2	14 $\pm$ 2
CI L/min/m2	2.8-3.4	5.3 $\pm$ 1.6	5.1 $\pm$ 1.4	5.3 $\pm$ 2.0	4.6 $\pm$ 1.0*
LVSW gm/m2	50-62	56 $\pm$ 8	55 $\pm$ 12	55 $\pm$ 14	53 $\pm$ 5
O2 Del ml/min/m2	550-650	354 $\pm$ 34	341 $\pm$ 104	364 $\pm$ 54	375 $\pm$ 132
VO2 ml/min/m2	115-215	99 $\pm$ 23	92 $\pm$ 20	92 $\pm$ 9	112 $\pm$ 18*
Hct%	36-48	14.1 $\pm$ 6.0	14.1 $\pm$ 6.0	14.1 $\pm$ 6.0	14.1 $\pm$ 6.0
Fct%	0	0	0	5.3 $\pm$ 0.5	5.3 $\pm$ 0.5
FiO2	21-100	21	80	35 $\pm$ 18	100
PaO2 torr	92-98	82 $\pm$ 13	299 $\pm$ 49	103 $\pm$ 30	363 $\pm$ 91
CaO2 ml/dl	17-20	7.2 $\pm$ 2.0	7.3 $\pm$ 3.2	7.2 $\pm$ 2.2	8.1 $\pm$ 2.8**
PvO2 torr	34-42	37 $\pm$ 2	44 $\pm$ 5	42 $\pm$ 3	70 $\pm$ 27*
CvO2 ml/dl	12-15	5.2 $\pm$ 1.7	5.3 $\pm$ 2.0	5.3 $\pm$ 2.0	5.7 $\pm$ 3.5*
v Sat %	72-78	69 $\pm$ 5	78 $\pm$ 3	75 $\pm$ 2	90 $\pm$ 6*
P tcO2 torr	65-85	56 $\pm$ 14	299 $\pm$ 96	92 $\pm$ 42	410 $\pm$ 113

* p<0.05   Transcutaneous/arterial O2 correlation

** p<0.005   Correlation coefficient, r = 0.96
Slope, s = 1.15
intercept, i = 28
number of data sets, n = 89

in Table XII for the four parts of the study: control data before Fluosol at low and high FiO2, and after Fluosol infusion at low and high FiO2. These five patients were in a hyperdynamic state to compensate for their anemia as seen by the high values of heart rate and cardiac index. They were able to achieve nearly 60% of the normal rate of oxygen delivery which brought them to within 86% of the normal range of total body oxygen consumption (VO2). Except for the most severely anemic patient (Hb - 1.9 gm %), who has always treated with supplemental oxygen, the four other patients tolerated breathing room air in spite of mean Hct and CaO2 values nearly 1/3 of normal (Hct - 14.1 $\pm$ 6.0%, CaO2 = 7.2 $\pm$ 2.0 ml/dl). When the patients were treated with high FIO2 using a tight fitting, nonrebreathing mask, there were no statistically significant changes in hemodynamic parameters. The PaO2 increased from 82 torr to 299 torr. Conseqently, the CaO2, PvO2, CvO2, and SvO2 all increased. The PtcO2 responded quickly and linearly to all the changes in FiO2. The 95% response time was approximately 2 minutes. A linear regression between PaO2 and PtcO2 values produced a correlation coefficient of 0.96.

Effects of Fluosol Infusion:

Prior to the infusion of Fluosol, a 0.5 ml test dose was given intravenously to each patient. Two of the seven patients had symptomatic reactions following the test dose and are presented in detail in the appendix - 'Clinical Reactions'. The other five patients completely tolerated both the Fluosol test dose and the infusion, demonstrating only gradual increases in the WP. Two patients were treated with furosemide when the WP reached 18 cm H2O. As stated previously, complete blood counts were obtained immediately before and after the Fluosol test dose in three patients. All three patients had an immediate and transient fall in white blood count (WBC). The values decreased to 35% of baseline at 5 minutes after the test dose and returned to baseline WBC at 10 minutes. This hematologic response will also be described in more detail in the appendix.

TABLE XIII Fluorocrit Determination

Patient No.	Sex	Fluosol	Blood Volume#	Measurement FCT	Calculated FCT+	GC*
S.E./9	M	1,500	4.0	3.2	5.5	
D.G./7	F	1,000	3.4	2.7	4.5	
B.W./13	F	1,500	4.2	2.4	5.3	5.39
K.W./12	M	1,500	4.0	2.8	5.4	
H.R./8	F	2,000	4.9	3.0	5.8	
				2.8 $\pm$ 0.3	5.3 $\pm$ 0.5	

\# Blood Volume Index:
  M 2.74 F 2.37 (L/M2 body surface area)

+ FCT $= \dfrac{\text{Fluosol Volume}}{\text{blood volume + fluosol volume}}$ x 0.2

* Determined by gas chromatography

OXYGEN CONTENT INCREASE
DUE TO THE PERFLUOROCHEMICAL
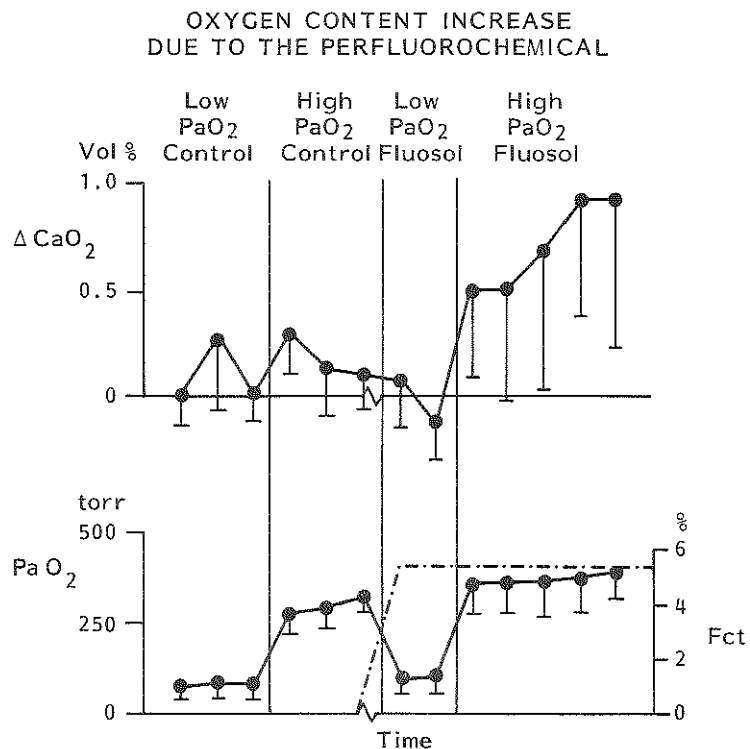
Fig 10 The time course of CaO2-Cao2c (upper graph), PaO2 and Fct
        (lower graph) are presented above. The difference between
        CaO2 and caO2c represents the additional oxygen carried solely
        by the presence of the PFC. Note, this difference becomes
        significant only when Fluosol is present with high PaO2
        values.

After the 20 ml/kg Fluosol infusion, the patients breathing low FiO2 (35 $\pm$ 18%) demonstrated no significant hemodynamic or oxygen transport changes other than an increase in WP (5.4 $\pm$ 1.0 to 13 $\pm$ 4 cm H2O) and fluorocrit (0 to 5.3 $\pm$ 0.5%). None of the other changes in monitored values could be attributed to the addition of Fluosol (Table XII).

Fluorocrit values peaked approximately one hour after the completion of the infusion, decreased to half the maximal value at 24 hours, and were undetectable at 48 hours. The measured Fct values were half the expected values, 2.8 $\pm$ 0.3% versus 5.3 $\pm$ 0.5% (Table XIII), based upon the previous clinical experience, published literature and a calculation derived from the administered volume (calculated fluorocrit = Fctc). This was presumably due to the inability of the hospital centrifuge to attain the required speed of 12,000 rpm. In a patient where the Fct was determined from multiple samples by gas chromatography (FctGC) the FctGC values agreed with the Fctc values, Fct 2.8%, Fctc = 5.39% (Table XIII).

When the patients were ventilated with 100% oxygen there were several statistically significant hemodynamic and oxygen transport changes. The VO2 increased from 92 to 112 ml min-1 m-2, while the CaO2 increased from 7.2 $\pm$ 2.2 to 8.1 $\pm$ 2.8 ml/dl at a PaO2 of 363 $\pm$ 91 torr (Table XII). This increase in CaO2 was sigificantly (p $<$ 0.005) greater than the calculated CaO2 value assuming no Fluosol (CaO2c) (Table XIV). Figure 10 presents the changes in CaO2 during the course of the study. The difference between CaO2 and CaO2c is the oxygen carried solely by the PFC. The difference between these two oxygen contents becomes significant only after Fluosol at high PaO2 values. This increase in oxygen content, due solely to the PFC, was approximately 0.7 ml/dl at PaO2 = 363 $\pm$ torr and a Fctc of 5.3 $\pm$ 0.5%. During this time the SvO2 reached 90 $\pm$ 6%.

Table XV presents the percentage of VO2, O2 Del and CaO2 carried by the PFC at its peak effectiveness (at maximal Fct and PaO2). The PFC supported 24 $\pm$ 7% of the VO2 and 7 $\pm$ 3% of the O2 Del and CaO2. In the most severely anemic patient the PFC was responsible for 26% of the VO2 and 12% of the O2 Del and CaO2.

Table XIV   Oxygen Content Comparison

	1 CaO2	2 CaO2	3 CaO2F	PaO2	n
Without Fluosol	7.2 + 2.8	7.2 + 3.0	-	208 + 118	32
With Fluosol at low PaO2	6.8 + 3.2	7.2 + 2.2	7.0 + 3.3	10.3 + 30	10
With Fluosol at high paO2	7.5 + 2.7*	8.1 + 2.8	363 + 2.7	363 + 91	47

1. Calculated by standard formulae, P1O2, Hb and O2 saturation assuming no Fluosol.

2. Measured with Lexington Institute, LEX-O2-Con-TL.

3. Calculated with Fluosol, CaO2 = CaO2c + FCT x PaO2 x 3.315 x 104

    *With Fluosol at high PaO2, CaO2 is statistically significant ($P<0.005$) different
    from CaO2 and CaO2F (by student t test, the difference between the means: Paired
    data with unknown population variances).

There were no significant changes in arterial carbon dioxide partial pressure (PaCO2) or pH. Throughout the entire study period each patient's oxygenation status was continuously and noninvasively monitored with the PtcO2 sensor.

In Table XIV, CaO2 is determined in three ways and compared during three phases of the study. CaO2c is the content calculated by standard formulas assuming no Fluosol is present, CaO2 is the content directly measured by the LEX-O2-CON-TL and CaO2F is the calculated content, taking into account the oxygen carried by the PFC. Before Fluosol, CaO2c and Cao2 are not significantly different. At low PaO2, after Fluosol, all three oxygen content determinations are not significantly different. However, at high PaO2, after Fluosol, CaO2 and CaO2F are still not significantly different, but both are significantly (p<0.005) higher than CaO2c.

Discussion

Fluosol is known to transport oxygen and has supported life in experimental animals which have undergone exchange transfusion to Hct of 1%. We recently reported a case study describing extensive hemodynamic monitoring during Fluosol administration in a severely anemic surgical patient. This paper presents statistically significant evidence of the amount of oxygen transported by the PFC alone when Fluosol-DA 20% is used in the clinical setting.

Because PFCs carry oxygen by direct solubility, as does the plasma, at high PaO2 values the tissues will extract 75 to 80% of this dissolved oxygen before any significant oxygen is released from the hemoglobin. This is evidenced by the high SvO2 noted in these patients after Fluosol administration, SvO2 = 90 ± 6% at PaO2 = 363 ± 91 torr. In two patients the SvO2 reached 97%. It also must be considered that these results were achieved with a fluorocrit of only 5%. In addition to the statistically significant increase in CaO2 and SvO2, the only other variable with a significant increase was the VO2.

There are two reasons why the oxygen transported by the PFC emulsion might be more readily utilized by the tissues than the oxygen bound to hemoglobin. First, since the oxygen extracted from the blood is at a higher PO2, there is a greater PO2 gradient for diffusion into the tissue. Second, the PFC emulsion particle size is approximately 0.1 micron. This small size (1/70 the size of the RBC) would allow for flow through small capillaries at faster rates. Both of these phenomena would have contributed to the increased VO2 found in this study. Glogar et al. (1981) demonstrated a substantial decrease in myocardial infarction size in experimental animals pretreated with PFC emulsions at high FiO2 values.

The patients in this clinical trial were all hyperdynamic, mean C.I. = 5.3 $\pm$ 1.6 L/min/m2, to compensate for the decreased CaO2 due to the anemia. The mean C.I. decreased after Fluosol treatment to 4.6 $\pm$ 1 L/min/m2, but the decrease was most dramatic in the more severely anemic patients, i.e. HB 6 gm%. These changes were somewhat confounded by the changes in plasma volume with Fluosol treatment, WP 5.4 cm H2O before and 14 cm H2O after Fluosol. If the patients had their control data taken at comparable WPs the decrease in C.I. might have been more dramatic. This was not clinically feasible.

Note that, as expected, the only significant rise in CaO2 comes after administration of Fluosol at high PaO2 values. This is about 0.7 volume % or ml per deciliter at 400 torr at a fluorocrit of 5%. Although this increase may appear small, when taken in the context of severe anemia, and considering the consumable oxygen, which must be at a high enough PO2 to diffuse into the tissues, this small vol % of oxygen can be very significant. Since normal arterial blood oxygen content (CaO2) is 17 to 20 vol %, an increase of 0.7 vol % would not seem to be very significant. But in cases of severe anemia this 0.7 vol % may mean the difference between survival and non-survival. At normal blood flow rates (cardiac index, C.I.) the body consumes about 4 to 5 vol % (arteriovenous difference (avDO2)) of the 17 to 20 vol % oxygen during each circulation through the peripheral vascular bed. Therefore, even in a normal

104

patient, this 0.7 vol % of oxygen comprises approximately 17% of the consumed oxygen. In severely anemic patients, like those in this study, whose avDo2s were approximately 2-3 vol %, this same 0.7 vol % carried by Fluosol (PFC) accounts for 20-40% of the consumed oxygen.

The PtcO2 monitor was extremely valuable in treating these anemic patients. It allowed us to minimize blood gas sampling and to take the samples at the appropriate times; i.e. when the trend in PtcO2 values alerted us to changes in PaO2. When the most anemic (Hb 1.9%) patient was first evaluated he was in acute respiratory failure and needed preload adjustment and multiple PEEP studies before his PaO2 was sufficiently high enough to potentially benefit from Fluosol therapy. During this time we were able to titrate PEEP values without blood sampling by following PtcO2 and C.I.

Clinical Safety:

In five patients there were no symptoms associated with Fluosol therapy. One patient had very vague, subjective symptoms which lasted less than one minute. One other patient had a significant clinical reaction to a test dose, which resolved itself without treatment within 3 minutes. The underlying mechanism is unclear but probably involves the activation of a self-limiting complement cascade. The alternative pathway of the complement system has been implicated as initiating the reaction. The acute fall in WBC, noted in all patients subsequently evaluated from hematologic changes, might be involved in the same mechanism. It is important to note that, in these three patients, there were no hemodynamic changes associated with hematologic changes. Similar immunological activation has been recently reported with patients receiving hemodialysis or cardiopulmonary bypass. This is an area in need of further investigation.

Hemodynamic and Oxygen Transport Effects:

Fluosol has been shown to significantly increase the CaO2 (0.7 ml/dl at Fct

of 5% and a PaO2 of 363 torr) in these patients. This increase in CaO2 produced improved hemodynamics and oxygen utilization; VO2 increased with a decrease in C.I. In all cases the patients were objectively improved and consequently had an increased margin of safety for their surgical procedure. From the data showing the haemodynamic and oxygen content changes after Fluosol we have demonstrated that Fluosol is carrying the expected oxygen and that this amount of oxygen is clinically significant. The clincial significance in these patients increased with decreasing hemoglobin. It must be pointed out that none of these patients had significant cardiac disease and they were able to compensate for the severe anemia without cardiac decompensation. Obviously a patient with severe cardiac disease would not tolerate this severe anemia and might clinically benefit from Fluosol at even higher hemoglobin values.

Calculated CaO2:

Table XIV presents measured and calculated oxygen content values that allow a reasonable estimate of the CaO2 (with Fluosol) to be determined if the Hct, Fct, and PaO2 are known.

In conclusion, it appears that there is a future for PFC emulsions as a treatment for inadequate oxygen transport. This work demonstrates one possible indication for Fluosol therapy. In the future, other uses may prove valuable, i.e., carbon monoxide poisoning, acute myocardial infarction, cerebral vasospasm, or other acute microvascular oxygen transporting defects. However, the development of artificial red cell substitutes must proceed with cautious optimism until the acute and chronic side effects are more fully understood.

Significant Hemodynamic Reaction to the Fluosol test dose:

The fourth patient entering the study had a severe symptomatic and haemodynamic reaction to a test dose of Fluosol (Figure 11).

Approximately two minutes after receiving ½ cc of Fluosol, this 51 year old male with no known allergies complained of shortness of breath and a diffuse

106

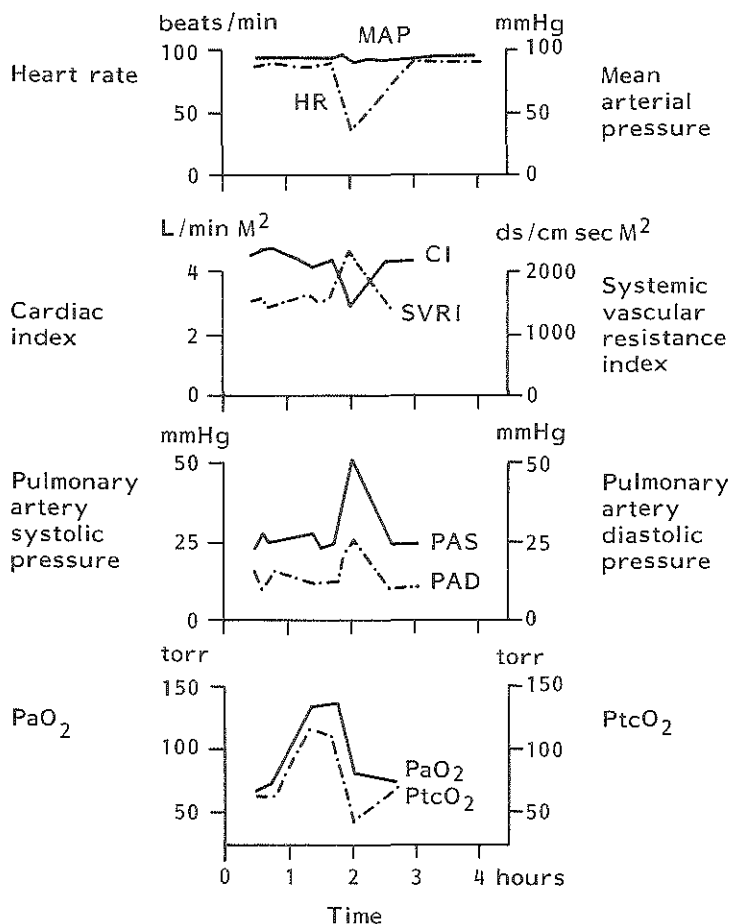SIGNIFICANT HEMODYNAMIC REACTION TO
A 1/2 CC TEST DOSE OF FLUOSOL DA 20%

Fig 11   The above four-part figure presents graphically the time
course of one patients significant hemodynamic reaction to a
½ cc test dose of Fluosol. Note the normotensive bradycardia
(upper) commenced with nearly compensating changes in CI and
SVRI (second from top). The pulmonary pressures increased
even more severely (second from bottom). The precipitous drop
in PaO2 could not be entirely attributed to the reaction
because the anxious patient removed his non-breathing oxygen
mask, although the larger drop in PtcO2 relative to PaO2 does
imply tissue hypoxia and is consistent with the increased
SVRI.

pressure pain of the chest. The patient became agitated but remained alert and cooperative. These symptoms were coincident with the following hemodynamic changes: normotensive bradycardia to a rate of 30 beats per minute, a 35% drop in cardiac output, a 50% increase in systemic vascular resistance, and a 100% increase in pulmonary artery systolic and diastolic pressure. The PaO_2 dropped, but this was due to the patient removing his oxygen mask. The $PtcO_2$ dropped in greater proportion, implying decreased peripheral oxygen delivery. The changes and associated symptoms gradually resolved over the next three minutes without treatment. The study was terminated and serial EKG's, cardiac enzymes and PaO_2 values revealed no resultant cardiac or pulmonary damage.

After this vasoconstrictive reaction, we consulted with Dr. Greg Vercellotti of the University of Minnesota, Hematology Department, who had been conducting research of the potential cause of a similar reaction seen in the first U.S. patient administered Fluosol at the University of Minnesota. Dr. Vercellotti had noted similar reactions in rabbits, with acute transient decreases in white blood cell and platelet counts during the reaction. He explained the reaction as an activation of complement through the alternative pathway which initiates a self-limiting cascade. The activation produces fragments which cause the WBC's to be surface active and marginate to the blood vessel walls, predominately in the pulmonary bed. This produces a transient five minute leukopenia. Of major importance was the finding that high-dose glucocorticoids inhibit granulocyte sequestration and affregation, at just the concentrations which appeared to obviate the pulmonary complications seen in the first patient. Utilizing this information, complete blood counts were taken before the test dose, and five and ten minutes after the test dose in subsequent patients.

Mild reaction to the Fluosol test dose:

The fifth patient entering the protocol also had a reaction to the test dose, but of a much milder type. The patient complained of a vague abdominal/chest pressure sensation which lasted less than one minute. The only objective changes

HEMODYNAMICS AND WBC DURING
MILD SYMPTOMATIC REACTION TO A
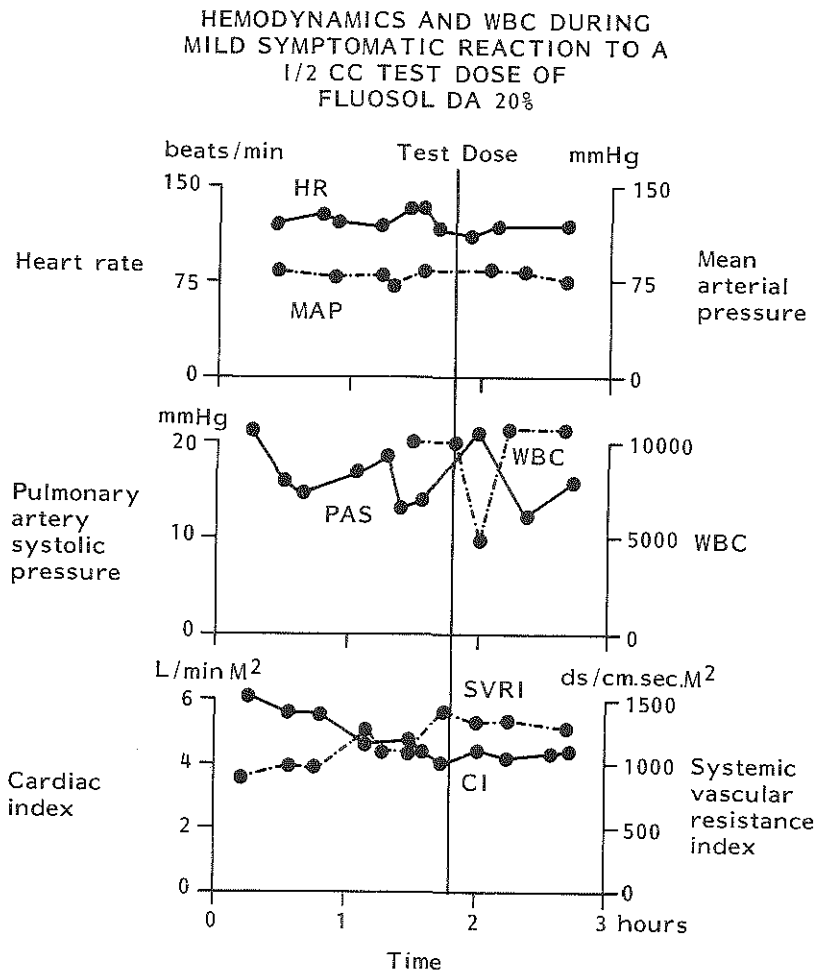1/2 CC TEST DOSE OF
FLUOSOL DA 20%

Fig 12   The above three part figure graphically presents the time
course of some of the monitored parameters of a patient who
had a very mild symptomatic reaction to the test dose of
Fluosol. There were no significant changes in HR and MAP
upper section) or CI and SVRI (lower section). The PAS did
not rise transiently and also corresponded to a dramatic drop
in WBC (middle section). This was the first patient in whom
WBC's were taken before and after the test dose.

were an increase in pulmonary artery systolic pressure (PAS),and a WBC drop from 10,000 to 3.600 and back to 10,000 at ten minutes. The heart rate, MAP, cardiac output and SVR all remained unchanged (Figure 12).

Several clinical and experimental observations suggested that these phenomena could be prevented in patients by pretreatment with corticosteriods or by combinations of drugs including corticosteriods (see below). The patient therefore consented to, and received, a 2.0 gram bolus (30 mg/kg) of Solu-Medrol IV and 50 mg of Benadryl IM, and was rechallenged with 0.25 ml Fluosol. The PAS again rose. Another 0.25 ml of Fluosol was administerd five minutes later, and the PAS increased further, with the patient reporting a very mild chest sensation but no shortness of breath or pain. Concomitant serial WBC counts taken over the entire course of Fluosol administration demonstrated a sharp transient and intermittent drop paralleling the rise in PAS, with a return to normal PAS pressure, comensurate with the recovery to a normal WBC count. Solu-Medrol blunted the extent of the phenomenon. Two additional test doses were administered during the next 1 to 1½ hours. The same response was observed physiologically, even though the patient no longer had any symptoms and did not complain of any discomfort. No further attempts were made to infuse Fluosol.

WBC changes after a test dose:

Neither of the last two patients entered into the study had symptomatic and hemodynamic reactions to the test dose but both had decreases in WBC's to a mean of 35% of baseline at five minutes, and all WBC's returned to baseline at 10 minutes. Platelet counts were taken in one patient and they followed the same pattern (Figure 13).

The clinical experience to date have indicated that adverse reactions are therapeutically manangeable. The possiblity that they may be predictable by in vitro testing of the patient's plasma is currently under investigation. It is of interest to note that these reactions have been far more common in the American experience than the Japanese. There are however, dietary differences which may

110

result in differences in blood cell functions between the Japanese and the Americans.
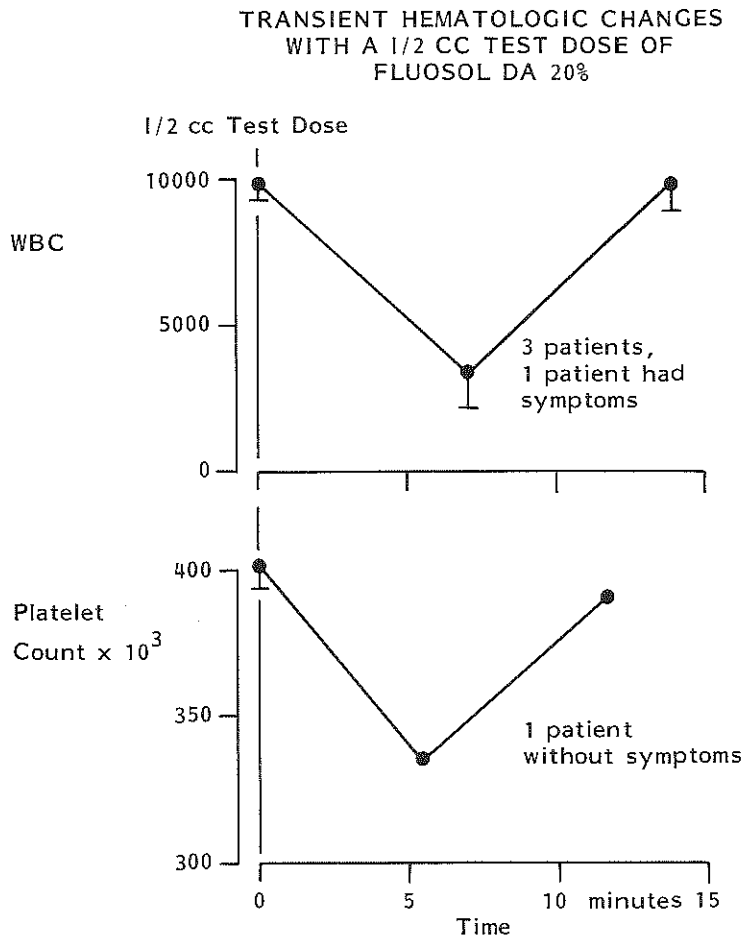
TRANSIENT HEMATOLOGIC CHANGES
WITH A 1/2 CC TEST DOSE OF
FLUOSOL DA 20%

1/2 cc Test Dose

WBC

3 patients,
1 patient had
symptoms

Platelet
Count x 10^3

1 patient
without symptoms

Time

Fig 13 The above figures present the time trend of WBC (upper
section) and platelet count (lower section) before and after
the ½ cc Fluosol test dose. These data were obtained from the
last three patients entering the study, none of which had
significant hemodynamic changes after the test dose.

CHAPTER VI

<u>DISCUSSION</u>

Surgery and anaesthesia can be efficiently and successfully performed in patients in whom homologous blood transfusions are either not available, or when the patient refuses to accept such a therapeutic modality due to religious objections. In order to embark on such unchartered grounds one must first assume the patient with a haemoglobin level far below 10 grams can indeed be operated on without serious complications.

By using lactated ringer solutions and/or starch preparations one can compensate for the lost volume, but not for the loss in oxygen carrying capabilities. Volume replacement can only improve the condition of an anemic, volume depleted patient to a certain extent, at which time, oxygen carrying fluids together with high oxygen tension must be instituted if the patient is to survive. Fluorocarbons with their considerably smaller particle size than a red blood cell, coupled with their extremely high affinity for oxygen, (which is dissolved in the solution rather than chemically bound as it is to hemoglobin), have been shown to be effective in performing this task.

In our laboratory and clinical studies Fluosol DA-20% has so far proved an excellent material with minimal side effects, which has been responsible for saving lives in anemic patients as well as opening new horizons in the treatment of myocardial infarctions, cerebral vascular accidents, and shock. In addition, it is proving to be a useful adjunct in the areas of reimplantation of severed extremities and of organ transplantations.

In clinical trials in the United States we have employed Fluosol infusions in a total of 17 patients whose haemoglobin concentrations varied from 1,6 to 7,2 gm per 100 ml. All patients received a test dose of 0.5 ml of Fluosol intravenously, preceeded by cortisone treatment. In all cases a short term leucopenia was observed which usually returned to normal after a few minutes.

In one case we observed bradycardia and pulmonary hypertension which resolved spontaneously. No complications other than these have been observed. Though reports of allergic reactions have been reported from Italy, no adverse reactions have been notified in reports from Japan on the use of Fluosol.

It is almost impossible to compare the results obtained in our series with those of others because, in all other studies fluosol was used an an adjunct to blood whereas in this series no blood was used and fluosol was used as a substitute for blood.

The surgical approach to a patient without blood transfusions as a foundation for intraoperative loss must start by reorienting our thinking toward minimising blood loss in the operating theatre. This can be accomplished successfully by employing hypotensive anesthesia, localised hypothermia and the extensive use of the electrosurgical knife or the laser apparatus. The shed blood is not discarded but rather collected intra-operatively, washed, and reinfused immediately, thus eliminating the need for banked blood. It must be viewed as axiomatic that the best blood one can infuse into a patient is his own and that the best way to eliminate the necessity for homologous blood transfusions is to minimise, if not totally eliminate, loss during surgery. The operating time is extremely important in determining the incidence of mortality and morbidity of the patient in general and the anemic patient specifically. To that end, techniques aimed at shortening operative time are employed in our daily practice and a continuous effort is directed towards the development of new and expeditious techniques.

The surgical techniques (which are discussed in Chapter II) include oesophageal stapling for the treatment of bleeding of oesophageal varices in the cirrhotic patient and internal iliac artery ligation for the treatment of uncontrollable bleeding of pelvic origin. The results that have been obtained in large numbers of patients are comparable to those obtained by other investigators using shunting procedures or massive blood transfusions.

To stimulate red cell production in patients whose bone marrow is stressed

beyond normal requirements of replacing a normal daily turnover of red blood cells, we have successfully employed, in 730 patients, the use of total dose iron dextran. The dose may be calculated using the formula: total dose of iron to be administered = .3 x weight in pounds of the patient x the deficit in haemoglobin. This therapy is combined with the administration of folic acid, vitamin B12, and anabolic steroid preparations.

Anaesthetic techniques were modified so as to be able to successfully anesthetise the anemic patient with minimal side effects and better utilization of oxygen distribution while maintaining an adequate blood pressure for purposes of vital organ perfusions. We have attempted to minimize the use of inhalation anaesthesia and, whenever possible, employ regional block for pain control. When this approach was not possible, ketamine, diazepam, muscle relaxants, high oxygen tension and minimum amounts of isofluorane were employed. Consultations between the anaesthesiologist and surgeon preoperatively, have been directly responsible for tailoring the appropriate anaesthetic and surgical approach to the specific patient and thus decreasing the overall mortality and morbidity.

Our experience with 5000 major surgical procedures in Jehovah's Witnesses' has demonstrated that anaesthesia and surgery can be carried out on patients with minimal reliance on the blood bank for intraoperative fluid replacement. It must therefore be assumed from this vast clinical experience obtained from patients (who can be viewed as a control group when compared to the general patient population in whom homologous transfusion are liberally employed), that perhaps clinicians tend to overtransfuse bank blood because it is readily available and not necessarily because the patient requires it. In the day and age of ever decreasing blood supply, which causes periodic shortages and necessitates cancellations of elective surgery, when absolute screening tests for hepatitis, and acquired idiopathic immune deficiency syndrome are still not available, we must learn from the data obtained from this control group and employ the lessons learnt to the benefit of all. We must deduce that blood

transfusions should only be given to patients who show the clinical manifestations of decreased oxygen carrying capacity and not necessarily to people with low hemoglobin concentrations. This philosophy will save resources, money and, hopefully, many lives.

CHAPTER VII

SUMMARY

Chapter I - The aims of the study are explained in relation to the need to reduce reliance on homologous blood transfusions.

Chapter II - Major surgery in Jehovah's Witnesses has been accomplished with mortality and morbidity figures that are comparable to those employing blood transfusions. We have employed in our approach the use of hypotensive anaesthesia, autotransfusion, localised hypothermia, the extensive use of the electrocautery and laser as well as modified surgical instrumentation in the drive to reduce operating and anaesthetic times. To aid in replacing lost red blood cell mass we have employed total dose intravenous iron dextran. Fluosol DA-20% was employed in patients having need of greater oxygen carrying capacity. Two specific approaches to special hemorrhagic problems which were frequently encountered (oesophageal varices, and pelvic bleeding) and their results are discussed.

Chapter III - A discussion is presented, of the specific problems with which the anaesthesiologist is confronted when presented with an anemic patient in whom homologous blood transfusion is not possible. The technique to solve this dilemma is illustrated employing regional block as well as intravenous ketamine, diazepam, and muscle relaxant. Anaesthetic problems faced by the anaesthetist in dealing with the anemic patient have been successfully overcome.

Chapter IV - Utilization of intraoperative autotransfusions to eliminate the need of transfusing banked blood in the various surgical subspecialties is discussed and the various apparatus to accomplish this modality of autologous blood replacement are discussed including the pros and cons of each such mechanical device.

Chapter V - Historical background of perfluorochemicals as well as the laboratory experimentation prior to clinical use as discussed in the literature, as well as

our early clinical results with this oxygen carrying media in Jehovah Witness patients is outlined. Our clinical experience using fluosol DA-20% has shown it to be extremely effective in changing the ischaemic changes which were manifested by the anemic patient. A specific case of a patient successfully operated at a haemoglobin of 1.6 is discussed in detail to illustrate this point. Additional laboratory research performed at E.U.R. with myocardial ischaemia induced in pigs is specifically noted. It has been proven that through dilution with fluosol DA-20% the myocardial zone could be reduced. A case report of a patient with the lowest haemoglobin yet recorded receiving fluosol is analysed.

In summary we can conclude as our introductory chapter has postulated that major surgery and anaesthesia has been safely conducted in 5,000 patients without the use of homologous blood transfusions. Fluosol can be used effectively as a blood substitute in anemic patients and could possibly also play a role in the prevention of ischemic changes of organs.

SAMENVATTING

In de introductie van de thesis wordt naar voren gebracht, dat het doel van dit onderzoek is homologe bloedtransfusies bij operaties te vermijden. Dit wordt bereikt door bloedingen tijdens de operatie met speciale technieken te beperken en eventueel optredend bloedverlies met autotransfusie of bloedvervangende middelen aan te vullen.

In hoofdstuk II van deze thesis wordt aangegeven, dat chirurgie en anaesthesie veilig kunnen worden uitgevoerd bij patiënten zonder het gebruik van homologe bloedtransfusies. Dit werd aangetoond met 5500 operaties bij Jehova's getuigen. Chirurgische ingrepen bij Jehova's getuigen gaan gepaard met een hogere mortaliteit en morbiditeit dan bij de patiënten-groep, waarbij het uitvoeren van bloedtransfusies mogelijk is. Uiteraard komen in de groep van Jehova's getuigen geen complicaties van bloedtransfusies voor. In deze groep patiënten werd gebruik gemaakt van hypotensie, autotransfusie, locale hypothermie, uitgbreid gebruik van diathermie, laser en aangepast chirurgisch instrumentarium, waarbij de operatietijd en de anaesthesietijd werden verminderd. Het bloedverlies werd aangevuld met intraveneuze toediening van Dextran. Bij patiënten bij wie de zuurstoftransport-capaciteit moest worden vergroot werd Fluosol-DA 20% gebruikt.

In hoofdstuk II worden verder twee speciale operatietechnieken beschreven voor speciale hemorrhagische problemen, die bij bloedende oesofagusvarices en bloedingen in het kleine bekken optreden.

In hoofdstuk III worden de speciale problemen besproken waarmee de anaesthesist te maken krijgt bij anaemische patiënten, bij wie een homologe autotransfusie niet mogelijk is. Speciale technieken, zoals regionale anaesthesie, inductie van hypotensie, en het gebruik van Ketamine/Diazepam samen met een spierrelaxans worden bij deze patiënten aangegeven.

Het gebruik van autotransfusie bij verschillende chirurgische ingrepen, om daarmee de noodzaak van bloedtransfusies te voorkomen, wordt in hoofdstuk IV

beschreven. De verschillende hiervoor benodigde technische voorzieningen worden besproken met al hun voor- en nadelen. Verder wordt in dit hoofdstuk het resultaat vermeld van het gebruik van intraveneuze ijzertoediening.

In hoofdstuk V wordt het nieuwe bloedvervangende middel fluorocarbon besproken. Allereerst wordt de historische achtergrond van de ontwikkeling van perfluorocarbonen in het dierexperimentele en klinische gebruik, zoals in de literatuur beschreven, uiteengezet. Eigen klinische resultaten met het gebruik van dit bloedvervangende zuurstofdragende middel bij Jehova's getuigen worden beschreven. Fluosol-DA 20% bleek buitengewoon effectief in anaemische patiënten. Een 'case report' wordt gegeven van een patiënt die met succes werd geopereerd bij een Hb van 1,6 gr. %. Resultaten van experimenten met fluorocarbon bij varkens worden weergegeven. Het effect van Fluosol-DA 20% werd getest in een experimenteel model waarbij ischemie van het hart werd geïnduceerd bij varkens. Aangetoond werd, dat haemodilutie met Fluosol-DA 20% het ischaemische gebied in het myocard kon verkleinen.

Geconcludeerd kan worden, dat chirurgische ingrepen uitgevoerd kunnen worden zonder het gebruik van homologe bloedtransfusies. Fluosol kan effectief worden gebruikt als bloedvervangend middel bij anaemische patiënten en zou mogelijk ook bij de preventie van ischaemische veranderingen van organen een rol kunnen spelen.

Adams, J.E., Owens, G., Headrick, J.R., Munez, A., Scott, H.W.
Experimental evaluation of Pluronic F-68 (a non-ionic detergent) as a
method of diminishing systemic fat emboli resulting from prolonged
cardiopulmonary bypass. S. Forum 1959:10, 585.

Andrews, I.C. Legal, ethical and medical guidelines for Jehovah's Witnesses
in Surgery. Weekly Anesthesiology Update. 1980:2 Lesson 34.

Berlind, M. Hypogastric ligation: a lifesaving procedure. Int. Surg. 1966:
45(4), 420.

Blundell, J. Experiments on transfusion of blood. Medical Chir. Trans. 1818:
9, 56.

Bolooki, H. Treatment of Jehovah's Witnesses: Example of good care.
Miami Med. 1981:51, 25-26.

Bonnett, C.A., Lapin, R. Intraoperative Autologous transfusion in
Orthopaedics. Orthop. Review, 1981:10, 49.

Bouchardy, B., Manjo, G. Histolpathology of early myocardial infarcts. A
new approach. Am. J. Pathol. 1974:74, 301.

Boerema, I., Klopper, P.J., Holscher, A.A. Transabdominal ligation of the
oesophagus in case of bleeding oesphageal varices. Surg. 1970:67, 409.

Burch, L.E. Autotransfusion. Trans. South Surg. Ass. 1922:35, 25.

Burchell, R.C. Arterial physiology of the human female pelvis. Obstet.
Gynecol. 1968:31(6), 855.

Burchell, R.C. Physiology of internal iliac artery ligation. J. Obstet.
Gynecol. of Br. Common. 1968:75, 624.

Charnley, J. Total hip replacement. JAMA, 1974:230(7), 1025.

Chemoweth, D.E., Cooper, S.W., Hugli, T.E., Stewart, R.W., Blackstone, E.H.,
Kirkin, J.W. Complement activation during cardio-pulmonary bypass.
Evidence for generation of C3a and C5a anaphylatoxins. N. Eng. J. Med.
1981:304, 497.

Clark, L.C. Jr, Gollan, F: Survival of mammals breathing organic liquids equilibrated with oxygen at atmospheric pressure. Science, 1966:152, 1755.

Clark L.C. Jr. Whole animal perfusion with fluorocarbon dispersions. Fed. Proc. 1970:29, 1695.

Clark, L.C. Jr., Wessler, E.P., Miller, M.L., Kaplan, S.: Right versus straight chain perfluorocarbon emulsions for perfusion media. Microvascular Res. 1974:8, 320.

Clark, L.C. Jr., Kaplan, S., Emory, C., Wessler, E.P. In: Erythrocyte Structure and Function'. Ed: F.J. Brewer, Alan R. Liss Inc., New York, 1975, pp 589.

Clark, L.C. Jr., Weesler, E.P., Kaplan, S., Miller, M.L., Becker, C., Emory, C., Stanley, L., Becattini, F., Obrock, V. Emulsions of perfluorinated solvents for intravenous gas transport. Fed. Proc. 1975: 34, 1468.

Cooley, D.A. Open heart surgery in Jehovah's Witnesses. Am. J. Cardiol. 1971:13(6), 779.

Cooperman, M., Fabri, P.J., Martin, E.W., Carey, L.C. E.E.A. esophageal stapling for control of bleeding esophageal varices. Amer. J. Surg. 1980:140, 821.

Corssen, G. Personal Communication, 1982.

Cove, H,. Matoff, J., Sack, H.J. Autologous blood transfusions in coronary artery bypass surgery. Transfusion, 1976:16, 245.

Cowell, H.R., Swickard, J.W. Autotransfusion in children's orthopaedics. J. Bone and Joint Surg. 1974:56(a), 908.

Cushing, H., Davis, L.E. Blood replacement during and after major intra-cranial surgery. Surg. Gyn. Obstet. 1925:40, 310.

Craddock, P.R., Fehr, J., Brigham, K.I., Kronenberg, R.S., Jacobs, H.S. Complement and leukocyte-mediated pulmonary dysfunction in hemodialysis. N. Eng. J. Med. 1977:296, 769.

Danielson, G.K., Dubilier, L.D., Bryant, L.R. Use of Pluronic F-68 to diminish fat emboli and hemolysis during cardiopulmonary bypass. J. Thoracic Cardiovasc. Surg. 1970:59, 178.

Davis, N.J., Jennings, J.J., Harris, W.H. Induced hypotension for total hip replacement. Clin. Orthop. 1979:101, 93.

Delguercio L.R.M., Personal communication, 1981.

Dixon, J.L., Smalley M.G. Jehovah's Witnesses. JAMA, 1981:246, 2471.

Dundee, J.W., Lillburn, J.K. Ketamine-Lorazepam-attenuation of psychic sequelae of ketamine by lorazepam. Anesthesia, 1977:37, 312.

Dunphy, J.E. Ethics - Surgery, Bull. of Amer. Coll. Surg. 1978:6(63), 12.

Ebert, R.V., Stead, E.A., Gibson, J.G. Response of normal subjects to acute blood loss. Arch. Int. Med. 1941:68, 578.

Eckhardt, I.J., Gossett, T.C., Amstutz, H.C. Autologous transfusion and total hip replacement. Clin. Orthop. 1978:132, 39.

Erdmann, W., Frey, R, Madjidi, A. Beisbarth, A. Oxygen carrying versus non-oxygen carrying colloidal blood substitutes in shock. Symposium 'Care of the Multitrauma Patient' Nijmegen, September 1981. In: Injury, 1982:14, 70.

Finch, S., Haskins, D. Iron metabolism, henatotoiesis following phlebotomy: Iron as a limited factor. J. Clin. Invest. 1950:28, 1078.

Flynn, J.C. Intraoperative autotransfusion (IAT) in elective orthopaedic surgery. Meeting: Advancements of medical instrumentation. San Francisco. Surg. Practice News. 1982:19, 6

Gardner, B., Bivona, J., Alfonso, A., Herbsman, H.H. Major surgery in Jehovah's Witnesses. NY State J. Med. 1946:76, 765.

Geyer, R.P., Monroe, R.G., Taylor, K. Survival of rats perfused with a fluorocarbon-detergent preparation. In: Organ Perfusion and Preservation. Ed: J.C. Norman. Appleton Century Crafts, New York, 1968, 85.

Geyer, R.P., Monroe, R.G., Taylor, K. Survival of rats having red cells totally replaced with emulsified fluorocarbon. Fed. Proc. 1968:27, 374.

Geyer, R.P. In: Parenteral Nutrition. Eds: H.C. Meng and D.H. Laws. Charles C. Thomas, Springfield, Illinois. 1970, 339.

Geyer, R.P. Fluorocarbon-polyol artificial blood substitutes. New Engl. J. Med. 1973:289, 1077.

Geyer, R.P. Review of perfluorochemical-type blood substitute. Proc. Xth Intern. Cong. Nutrition-Symposium on PFC Artificial Blood, Kyoto, 1975, 3.

Geyer, R.P: 'Bloodless' rats through the use of artificial blood substitutes. Fed. Proc. 1975:34, 1449.

Glogar, D.H., Kloner, D.A., Muller, J., DeBoer, L.W.V., Braunwald, E., Clark, L.C.Jr. Fluorocarbons reduce myocardial ischemic damage after coronary occlusion. Science, 1981:211, 1439.

Gould, S. Red cell substitute, hemoglobin solution or perfluorochemical? J. Trauma. 1982:22, 736

Grant, F.C. Autotransfusions. Adult Surg. 1921:74, 253.

Grants Atlas of Anatomy, 1978, 7th edition.

Grover, F.L., Heron, M.W., Newman, M.M., Paton, B.C. Effect of a non-ionic surface-active agent on blood viscosity and plateley adhesiveness. Circulation, 1969:39 & 40(Supplement 1).

Highmore, W. Practical remarks on an overlooked source of blood supply for transfusion in post-partum haemorrhage. Lancet, 1874:1, 89.

Howlett, D.F., Sabiston, D.C. Fluid fluorocarbon as an oxygenator in an experimental extracorporeal circulation. Arch. Surg. 1965:91, 643.

Jehovah's Witnesses and the Question of Blood. Watchtower Bible and Tract Society, Brooklyn, N.Y. 1977, 1.

Johnson, A.G. Injection sclerotherapy in the emergency and elective treatment of oesophageal varices. Ann. R. Coll. Surg. Engl. 1977:59, 497.

Kelly, A.D. Aequanimitas, Can. Med. Assoc. J. 1967:96 432.

Kelly, H.A. Ligation of both internal iliac arteries for hemorrhage in hysterectomy for carcinoma uteri. Bull. Johns Hopkins Hospital, 1894:5, 53.

Kemmel van, M. Ligitor resection segmentaire et anastomose a l'aptareil. P.K.S. – 25, D.E., l'eosotage abdominale après hemorragie par rupture de varices eosophagiennes. Lille – Chir. 1974:29, 1.

Klebanoff, G., Watkins, D. A disposable autotransfusion unit. Amer. J. Surg. 1968:116, 475.

Klebanoff, G., Early clinical experience with a disposal unit for intra-operative salvage and reinfusion of blood loss. Am. J. Surg. 1970:120, 718.

Kylstra, J.A., Tissing, M.O., Maen van der, A. Mice as Fish. Trans. Am. Soc. Artif. Intern. Organs. 1962:8, 378.

Laks, H., Pilon, R.N., Klovekan, W.P., Anderson, W., MacCallum, J.R. O'Connor, N.E. Acute hemodilution: Its effect on hemodynamics and oxygen transport in anesthetized man. Ann. Surg. 1974:180(1), 103.

Lapin, R. Major surgery on Jehovah's Witnesses. Contemporary Orthopaedics, 1980:2(9), 147.

Lapin, R. The use of intravenous iron Dextran (Imferon) in the Jehovah's Witness patient. Dept. of Surgery, Bellflower City Hospital, Fountain Valley Community Hospital, April 1982.

Lapin, R. and Garcia, F. Is the blood bank the answer? Dept. of Surgery, Bellflower City Hospital, Fountain Valley Community Hospital, April 1982.

Lash, A.F., MacNerland, R.H. Comparison of the results of internal iliac and uterine artery ligation in Wertheim hysterectomy and pelvic lymphyadenectomy. Int. Surg. 1970:50(3), 344.

Little, D.N.Jr. Induced hypotension in anesthesia and surgery. Anesthesia, 1955:16, 320.

Lockwood, C.D. Autotransfusion. Surg. Clin. N. Amer. 1931:11, 1069.

Mallory, T.H., Kennedy, M. The use of banked autologous blood in total hip replacement surgery. Clin. Orthop. 1976:117, 254.

Narengo-Rowe, A.J. The magic ten grams of haemoglobin. Presented: Workshop on current concepts in hemotherapy. San Diego, Jan. 1982.

Massachusetts General Hospital Report. Presented: Conference on Autotransfusion, Indiana University Medical Center, October 1982.

Milles, W., Langston, H.T. Further experience with autologous blood transfusions. Ann. Surg. 1963:158, 333.

Miyauchi, Y., Inoue, T., Paton, B.C. Adjunctive use of a surface active agent in extracorporeal circulation. Circulation, 1966:33(Supplement 1), 71.

Moss, G. Fluid distribution in prevention of hypovolemic shock. Arch. Surg. 1969:98, 281.

Myhre, B.A. Fatalities from blood transfusions. JAMA, 1980:244, 1333.

Naito, R., Yokoyama, K. Perfluorochemical blood substitutes Fluosol-43, Fluosol-DA 20% and 35%. Technical Information Service No. 5. (The Green Cross Corporation), 1978.

Ohyanagi, H., Sekita, M., Toshima, T., Kawa, Y., Mitsuno, T. Exchange transfusion with perfluorochemicals in monkeys. Proceedings: Symposium Res. on PFC in Medicine and Biology, Stockholm 1977.

Okamoto, H., Yamanouchi, K., Yokoyama, K. Retention of perfluorochemicals in circulating blood and organs of animals after intravenous injection of their emulsions. Chem. Pharm. Bull. (Tokyo), 1975:23, 1452.

Okamoto, H., Iwai, M., Tsuda, Y., Yokoyama, K. Changes of particle size of perfluorochemical emulsion in circulation. Proc. Xth Intern. Cong. Nutrition-Symposium on PFC Artificial Blood, Kyoto, 1975, pp73-82.

Orloff, M.J., Charters, A.C., Chandler, J.G., Condon, J.K., Grambort, D.E., Modaffer T.R., Levin, S.E., Brown, N.B., Sviokla, S.C., Knox, D.G. Portacaval shunt as emergency procedure in unselected patients with alcoholic cirrhosis. Surg. Gynecol. Obstet. 1974:141, 59.

Orloff, M.J. Emergency treatment of variceal haemorra. Canadian J. Surg.
    1979:22, 550.

Ott, D.A., Cooley, D.A. Cardiovascular surgery in Jevohah's Witnesses.
    JAMA 1977:238, 1256-58.

Papaloucas, A.C. Extraperitoneal ligation of the internal iliac arteries.
    Int. Surg. 1972:57(2), 162.

Paton, B.C., Grover, F.L., Heron, M.W., Bess, H., Moore, A.R. The use of
    a nonionic detergent added to organ perfusates. In: Organ perfusion and
    preservation. Ed: J.C. Norman. Appleton Century Crafts, New York, 1968,
    pp105-120.

Pelosi, M.A., Lanser, A., Li, T.S. Internal iliac artery (hypogastric)
    ligation for control of obstetric and gynecological hemorrhage.
    J. Med. Soc. N.J. 1976:74(4), 297.

Reeves, J.G., Erdmann, W., Mardix, M., Karp, R.B., King, M., Lell W.A.
    Evidence for existence of intramyocardial steal. Oxygen Transport to
    Tissue - III, 755-760. Eds: Silver et al. Plenum Press, New York-London,
    1978.

Rinecker, H., Danek, N. Operative Behandlung blutender Oesophagus Varizen
    durch eine subkardiale Blutsperre mittels transmuraler maschineller
    Klammerung. Chirurg, 1975:46, 87.

Robinson, C.E.G., Bell, C.N., Sturdy, J.H. Possible association of
    malignant neoplasm with iron-dextran injection. Br. Med. J. 1960:2,
    648.

Roen, P.R., Velcek, F. Extensive urologic surgery without blood transfusion.
    NY State J. Med. 1972:72, pp 2524-2527.

Rosenblum, W.I. Fluorocarbon emulsions and cerebral microcirculation.
    Fed. Proc. 1975:34, 1493.

Rose, M.C. Cellular biology-osmotic behavior of red corpuscles in a non-
    ionic surfactant solution: 'Pluronic F-68'. C.R. Acad. Sci. (Paris),
    1966:263, 1615.

Rush, B, Eiseman, B. Limits of non-colloid solution replacement in experimental hemorrhage shock. Ann. Surg. 1967:165, 977.

Sack, R.A. Bilateral internal iliac (hypogastric) artery ligation to control obstetric and gynecological hemorrhage. A ten year review at the community hospital level. Am. J. Obstet. Gynecol. 1973:116(4), 493.

Shinagawa, S., Nomura, Y., Kudoh, S. Full term deliveries after ligation of bilateral internal iliac arteries and infundibulopelvic ligaments. Acta. Obstet. Gynecol. Scand. 1981:60(4), 439.

Sloviter, H.A., Kamimoto, T: Erythrocyte substitute for perfusion of brain. Nature, 1967:216, 458.

Staples, P.P. Letter: Bilateral hypogastric artery ligation. Am. J. Obstet. Gynecol. 1973:117(6), 864.

Stillman, R.M., Gottlieb, B.S. Sawyer, P.N. Alleviation of autotransfusion-induced haemotological damage by corticosteriods. Br. J. Med. 1980:67, 99.

Suguira, M., Futagawa, S. Further evaluation of the Suguira procedure in the treatment of esophogeal varices. Arch. Surg. 1977:112, 1317.

Thompson, G.E., Miller, R.D., Stevens, W.C., Murray, W.R. Hypotensive anesthesia for total hip arthroplasty. Anesthesiology, 1978:48, 91.

Ties, H.J. Zur Behandlung der Extrauteringravidität. Zbl. Gynaek 1914:38, 1190.

Tremper, K.K., Lapin, R. Hemodynamic and oxygen transport: Effects of a perfluorochemical blood substitute. Crit. Care Med. 1980:8(12), 738.

Tremper, K., Lapin, R., Levine, E., Freidman, A., Shoemaker, W.C.: Hemodynamic and oxygen transport effects of a perfluorochemical blood substitute, Fluosol-DA (20%). Crit. Care Med. 1980:8(12), 738.

Tremper, K.K., Lapin, R., The preoperative treatment of severely anemic patients with a perfluorochemical oxygen transport medium, Fluosol-DA 20%. Dept. of Anesthesia, UCLA Medical Center, 1981.

Tremper, K.K., Shoemaker, W.C. Transcutaneous PO2 monitoring of adult patients while haemodynamically stable and during progressive low flow shock. Crit. Care Med. 1981:9, 706.

Turner, R.S. Autologous blood for surgical transfusions. J. Bone and Joint Surg. 1968:50(a), 834.

Vercelloti, G.M. Hammerschmidt, D.E., Craddock, T., Jacob H.S. Activation of plasma complement by perfluorocarbon artificial blood: Probable mechanism of adverse pulmonary reactions in treated patients and rationale for corticosteriod prophylaxis. Blood, 1982:59, 1299.

Walker R.M. Oesophageal transection for bleeding varices. Surg. Gyn. Obstet. 1964:118, 323.

Wallerstein, R.O. Intravenous iron-dextran complex. Blood, 1968:32, 690.

Warren, W.D., Zeppa, R., Fomon, J.J. Selective trans-splancnic decompression of gastro oesphageal varices bydistal spleno-renal shunt. Ann. Surg. 1967:166, 437.

The Watchtower, 1978:99, (June 15) 39.

Wexler M.J. Treatment of bleeding oesophageal varices by transabdominal oesophageal transection with the E.E.A. stapling instrument. Surg. 1980: 88, 406.

Wretland, A. Complete intravenous nutrition. Nutr. Metabol. 1972:14, 1.

Wright, E.S., Sarkozy, E., Dobbel, A.R.C., Murphy, D.R. Fat globulemia in extracorporeal circulation. Surgery 1963:53, 500.

Yokoyama, K., Suzuki, A., Utsumi, I., Naito, R. Determination of particle size distribution of fluorocarbon emulsion by means of centrifugal sedimentation. Chem. Pharm. Bull. (Tokyo) 1974:22, 2966.

Yokoyama, K., Yamanoucki, K., Murashima, R. Excretion of perfluorochemicals after intravenous injection of their emulsion. Chem. Pharm. Bull. (Tokyo), 1975:23, 1368.

128

Yokoyama, K., Yamanouchi, K., Watanabe, M., Matsumoto, T., Murashima, R.
Daimoto, T., Hamano, T., Okamoto, H., Suyama, T., Watanabe, R.,
Naito, R. Preparation of perfluorodecalin emulsion, an approach to the
red cell substitute. Fed. Proc. 1975:34, 1478.

Yokoyama, K., Yamanouchi, K., Arimura, H., Naito, R. Further studies on the
fate of PFC's of Fluosol-DA following intravenous injection.
Proceedings: Symposium Res. on PFC in Medicine and Biology, Stockholm
1977.

Zsigmond E.K., Kothasy, S.P., Matsuki, A., Kelsch, R.C., Martinez, O.
Diazepam for prevention of the rise of plasma cortocholamine caused by
ketamine. Clin. Pharm. Ther. 1974:15, 223.

ACKNOWLEDGEMENTS

The writer of this thesis was born in 1941 in Tel-Aviv, Israel and is now a United States Citizen. He studied medicine at Manmouth College, New Jersey, and Indiana University, Indiana, obtaining his M.D. in 1968.

The same year he commenced his surgical training in the Maimonides Medical Centre in New York. He has boards in surgery, abdominal surgery, proctology, and neurological and orthopaedic surgery.

He presently holds appointments in California at the Fountain Valley Community Hospital, the Good Samaritan Hospital, Anaheim, and the Bellflower City Hospital.