THE EAST ANGLIAN BTS

TOWARDS THE YEAR 2000

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A PERSONAL VIEW

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A personal view on the developments in the East Anglia BTS
1990-1992

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The BTS has to innovate to survive because of the major implications of the introduction of recombinant proteins which will replace plasma-derived protein concentrates in the near future.
An important problem in relation to the planning of the future of the BTS is that we do not know when the rec. proteins will be introduced on the market; but that it all will have major consequences is clear. New promising results in increasing expression levels of Factor VIII in cell culture have been published recently in Nature and 3-5 years before the rec. Factor VIII will be on the market is a probably a good guess.

From the moment of introduction of rec.Factor VIII the volume of plasma collection will be down-regulated. The number of donations will then be determined by the needs for erythrocyte- or platelet-concentrates or polyclonal gammaglobulin preparations. Therefore it is sensible to reduce abuse of platelet concentrates, which is closely related to the high incidence of alloimmunization against HLA class I and platelet specific alloantigens combined with poor survival of donor platelets. Diminishing the degree of alloimmunization can be achieved by modifications in the preparation of our cellular concentrates.

It is my opinion that the future of a modern BTS will concentrate on the cellular components of blood, and maybe of other tissues. The knowledge of the centre in cell-processing, cell-culturing, modulation of cell-function and cell-preservation is extremely limited. By means of cooperative research programmes the centre should try to improve its capacities in this field, which will facilitate the integration of new activities in the field of Transfusion Medicine.

Instead of investing in its future, the centre still maintains activities (e.g. production of reagents with certain specificities) which are out of date. In areas where industry has proved to provide better quality at competitive prices and the reagent market will move from polyclonal to monoclonal reagents. The centre has to to redefine its tasks in close cooperation with the Regional Health Authority and the National Directorate.

Although my time has been rather short to form an impression of the overall organization of the centre and the level of performance, I hope that my personal opinion will stimulate the discussion about the future developments and changes which could and must take place.

Adaptation of the centre to the today's Standards of Transfusion Medicine and the possibility to start new service related activities within its organization is only possible, if the managerial structure of the BTS becomes more flexible, less hierarchical and more open. The centre should become more open-minded to new developments and it should be explained to the personnel why major modifications in the tasks of the centre are needed. It is a my personal wish to make the centre more service-minded.

To facilitate new developments we will try and pursue the creation of a strong research group, which actually will help to break down the walls between the fast moving fields of biomedical research and the classic transfusion service. We need support for this at all levels. We will try to merge the research programme with that of the immunology and the haematology groups on the Addenbrooke's site.

After these introductory generalizations I will try to create a clear picture of possible future developments. Because of the limited time I had for the preparation of this document detailed calculations of the financial consequences are not yet available. Furthermore my restricted knowledge of your language has certainly hampered me sometimes in giving a clear definition of the problems.

My general view on new developments is divided in the following chapters:

Chapter 1

Reduction of activities

1.1 Introduction: Some activities could be reduced without diminishing the quality of the service. The decision whether or not a particular activity or facility should be ended depends mainly on finances; although the social consequences can not be ignored. The relation with the personnel and the unions should be optimized so that there is a broad acceptance for the needs to change.

1.2 Reagents: Some of the erythrocyte typing reagents produced in the BTS do not meet the high standards realized by the industry. Industrial production is highly competitive and a lot of extra's, like training programmes are organized by the commercial firms. Because of the rapid introduction of monoclonal typing reagents, the polyclonal ones will lose their application within five years. I suggest a reduction of the activities in this field. However there where the centre can compete with industry in price and quality (cell panels, enzyme preparations, control cells) the service can be extended.

1.3 Washing-up facilities: The recycling of glass tubes, etc. is still maintained in the centre. Disposables have now been introduced in most transfusion centers for hygiene reasons- and most probably also for financial reasons.

1.4 Autoclaves: The autoclave capacity exceeds the needs. All blood products are processed in disposable plastics. The need for autoclave facilities is probably related to the recycling of cotton wool only. Both these activities can be reduced to a minimum needed for QA and R&D facilities.

1.5 Distilled water and saline: Both products are produced on site. The centre should either increase these activities (e.g. for the whole Region) or this activity should cease. The quality of the saline solution is far away from acceptable standards for GLP.

1.6 Canteen: A high percentage of the personnel is using the lunch facilities at the Addenbrooke's site. A more formal relation with the Addenbrooke's Hospital for this service would create the possibility to reduce the size of the canteen in the BTS. The service for the senior staff is out of proportion. One central coffee and tea service point for the staff and the donors is enough.

1.7 Private laboratories: Most of the senior staff members do have tailor-made laboratories for themselves. Working in splendid isolation does not result in top performance. Besides these laboratories are although completely equipped are ineffectively utilised. They should therefore be made available as soon as possible for new activities.

1.8 Administrative department: The number of secretarial and administrative people is rather high. On basis of my experiences with Dutch BTS's the ratio of administration/laboratory space seems to be completely out of balance.
A comparison with other centers could help us to decide how to improve the organization of the clerical work and whether a reduction in this sector is possible. Whether this can be realized will depend strongly on the level of computerization. A higher degree of compatibility between the word-processors, personal computers and the main-frame system is extremely relevant in this aspect.

.9 The donor sessions: The donor session organization is extremely expensive because all the teams are working from Cambridge-basis. The high costs for overnight stays in hotels and the long travelling distances can be reduced by the opening of a satellite centre, where donorteams are sited. Also donor sessions can take place on this new site. Because of its central position in the region and its large population Norwich seems preferable.

Chapter 2

2 Donor/BTS relation, a wish for improvement

2.1 Introduction: A donor who has once entered the BTS system should be motivated to remain donor. The investments needed to enter and remove a person from the system are high (administrative activities) Certainly when a donor is also phenotyped for red cell bloodgroups others than ABO and Rh(D), HLA class I and II and platelet alloantigens the invested capital is at least 400 pounds. Thus the relationship with such donors must be intensified. Besides the more frequent the donor blood of a particular donor has passed all the standard tests (virology and ABO/Rhesus typing) the better the safeguards will be that no mistakes are made.

2.2 Proposal: Thus I suggest to intensify the relation between the donors and the centre and such a programme will be profitable on short term. At the moment the donor turnover is too high and is partially responsible for the poor planning of the plasma production capacity. For some years various BTS's have started PR programmes to improve donor/BTS relation. Some suggestions for such a programme are:

i) the foundation of a donor society
ii) open days at the centre
iii) mailing of an information bulletin to all donors
iv) re-evaluating the rewarding system
v) introduction of an donor ID card (see later infra)
vi) increasing the number of donors which are bled at the premises of the centre
vii) intensification of the training programme of the donor attendants to make them aware of their crucial role as a bridge between the donor and the centre
viii) education in schools

2.3 Donor counselling: Since the number of screening tests for virology status and surrogate tests (ALT test) is steadily increasing, we are confronted with a major problem in the relation with our donors. An important task for the BTS is to protect the donor for adverse effects related with the donation. An increasing number of donors will not be allowed to donate because a particular screening test is positive. Rejection will in the majority of the donors cause concern about their general health. It is a moral obligation for the BTS to explain a donor why he or she was rejected and the consequences of the positive test(s). Close cooperation with the GP's and specialized counselors (in case of HI infection) is needed. Our attitude at the moment is based on "no information, no advice and no support". On ethical grounds there is a wish for improvement and a adequate counseling in the first phase by someone from the BTS will help us to improve the relation with our donors.

2.4. Conclusions: I realize that this is a very global plan to intensify our PR activities. The realization of these plans is however a must, because the donors are one of the two wings on which the BTS is flying. In the coming five years we must reduce the turnover rate. If a programme is initiated, the effect can be easily measured on an annual basis. As mentioned in my introduction of this paragraph this programme will be profitable on a short-term. To start PR activities more funds are needed.

Chapter 3

3 Automation/computerization

3.1 Introduction: The level of automation will increase further in the period 90-92. To optimize the computer main frame usage the possibility should be created to download main frame data onto personal computers (PC). This implies that the automation in the administrative and staff sector must be coordinated in close cooperation with the main frame developers.

3.2 Proposal:

3.2.1 P.C.'s: It is advisable to increase the number of PC's in the coming two years. No funds should be made available anymore to acquire administrative systems which will not be capable to communicate with the main frame system. If downloading of donorfiles onto a PC is possible donor data will be available at the place of donation. The mobile teams can modify the donor file during the sessions.

3.2.2 Donor ID cards: For donor identification a donor ID card could be introduced This card can be issued to each donor and will be a "constant reminder". The main characteristics of the donor would be stored on such a ID card. This will probably help to decrease the high rate of donor turnover.

3.2.3 Antenatal screening programme: The screening for irregular antibodies is done by an agglutination technique with automated reading of results. The pipetting work is still done manually and the volume of clerical work is enormous. Because of the size of this screening programme (about 200 samples/day, 10 tests per sample) automation is sensible. This means an investment in pipetting instruments and computer hardware for data management and storage and for the generation of the letters to the clinicians. Software is in development in Cardiff computer centre. Transfer of this programme is financially advantageous and implementation will be possible in short term. The ABO and Rhesus bloodgrouping of the antenatal department should be integrated with the fully automated bloodgrouping on the donordepartment. Therefore anticoagulated bloodsamples should be collected instead of clotted ones. For this purpose special tubes must be made available for the hosptals.

3.3 Conclusion: Since the planning and development of the main frame system is done by a consortium of BTS's further discussions will be needed to actually realize these plans. However extra funding seems appropriate and to support this I should like to refer to the letter of Dr Moore, dd 141189 in which he advises the region to stimulate the process of computerization and make available extra funds for this. The antenatal programme can be seen as separate entity because this programme is not related with the task of the main frame system - being information management for blood donors.
To realize optimal use of the computer systems and the introduction of the antenatal automation programme an extra person will be needed in the computer department. Investments in hardware will not be very profitable if there is not the capacity to familiarize the workers with the possibilities of the systems.

4 Component preparation

4.1. Introduction: After centrifugation cells and plasma are separated manually. Standardization of this procedure is essential for the quality of the plasma and the factor VIII yield and for the quality of the cell concentrates. As long as this handling is done manually inaccuracy is inevitable because of the high numbers of donations to be handled per day. Furthermore flexibility in the daily production capacity is restricted because of these manual procedures. Thus there is a friction between the wish to increase the collection of plasma for factor VIII production and a limitation in the handling capacity. At the moment about 40% of our blood is issued as whole blood. Whole blood transfusions are not indicated. Although component therapy might be more expensive, it is needed to become self-sufficient for protein concentrates and is generally accepted that the patient must receive only that component of which there is a deficiency. With repect to the use of plasma-derived protein concentrates the central production in BPL will be the safeguard for the patient with respect to transmission of infectious diseases. The plasma needed to become self sufficient is withheld from the national stocks because of our low level of component preparation. I advise the reduction of whole blood issuing to 0.05% of our total number of units collected in the coming two years.

4.2 Automated handling: Instruments have been developed which will perform the plasma and cell separation. Four of these Compomat's (20.000 pounds per system) would be capable of handling the daily output. The advantages of this system will be:

i) a higher flexibility in production capacity without a need for extra personnel
ii) buffy coat removal can be realized (see later infra).
iii) the production of leucocyte poor platelet concentrates will be possible (see later infra)

4.3. High speed centrifuges: Blood cells and plasma are separated by high speed centrifugation. Six of our centrifuges are too old to perform according to standard regulations. The effectiveness of the centrifugation is therefore poor and the quality of plasma and cell concentrates is not according to general accepted standards. The high speed centrifuges which are "out of date" must be replaced.

4.4 Storage temperature before processing: A certain percentage of our collected blood is however still transported at 4oC. Howwever there are no scientific data which support the general accepted idea that cooling of whole blood to 4oC direct after collection is beneficial to the quality of the cellular products or the plasma constituents (Factor VIII yield). In contrary cooling of whole blood is disadvantageous:

i) it reduces neutrophil activity and thus impairs the natural immune defense against bacterial contamination
ii) the functional capacity of platelets will be diminished
iii) the factor VIII concentration will diminish considerably

Whole blood can be stored at 20oC until component separation takes place without decreasing the quality of any of the blood-derived products.
The mobile teams should be equipped with devices for controlling the blood temperature at 20oC directly after collection. This will lower the costs because no expensive cooling equipment will be needed. The time between bloodcollection and processing must be minimized to improve the quality of the plasma.

4.5 Flowrate monitors: A minimal flowrate during blood collection must be realized to standardize quality of the bloodproduct and also importantly for the safety of the donor. Cheap flowrate controllers can be clipped on the sampleline and, by measuring the temperature of the blood, an indirect but sensitive indicator is obtained for the flowrate. These devices should be provided to the mobile teams.

4.6 Equipment for the mobile teams: After collection of blood the units are transported in crates of poor quality. A budget is needed for improvement of the sort of equipment used on the sessions. I advise to increase the use of disposables for hygienic and safety reasons.

4.7 Storage temperature after processing: Blood-components must be stored under strictly temperature controlled conditions.

Red cells: The storage facilities of the red cell concentrates at 4oC are adequate. Storage facilities for autologous blood are not available and because the number of autologous transfusions will increase in the future a separate storage facility is needed.

Platelets: Platelet concentrates must be stored at 20oC. The fluctuations of the temperature in the room, where the platelets are stored is not acceptable. A temperature controlled cabinet for platelets which are ready to be issued is allegedly arriving. However the high temperatures during the production procedure are not acceptable because of the increased risk for bacterial growth.

Plasma: Plasma is frozen as soon as possible after preparation at temperatures below 30oC, before it is transported to the BPL or issued to the hospitals. The freezing capacity for plasma is restricted and therefore an increase in our plasma production cannot be realized. An extra investment in three blastfreezers has to be made to adequately respond to the national plasma requirements. The storage space below 30oC is also to limited.

4.8 Conclusion: The automation of component preparation is of crucial importance with regard to the flexibility in our plasma collection capacity and the increase of the quality of the cell concentrates (next chapter) can be realized more easily when important steps in automation has been made. Investments in capital goods are needed to remove certain bottle necks and to provide the BPL with the required kg of plasma.

5 Adaptation of the quality of cell concentrates

5.1 Introduction: Transfusion reactions caused by alloantibodies against bloodgroups on leucocytes is one of the serious side effects of blood transfusion (high fever, acute respiratory distress syndrome). Also an immunomodulatory (immunosuppressive) effect of leucocyte transfusion has been well established, and is even used to improve graft taking in kidney transplantation. However in patients with cancer this immunosuppressive effect could be responsible for a shorter survival.
Furthermore granulocytes have a short lifespan in vitro and the toxic content (toxic granule enzymes) of the granulocytes which are released upon cell lysis decrease the overall quality of the cell concentrates during storage. Aggregate formation in cell concentrates is mainly triggered by dying granulocytes.
Alloimmunisation against HLA class I antigens is one of the main reasons for poor survival of donorplatelets. The frequency of platelet transfusions in an alloimmunized patient can increase from ten to fifteen donor units per week to 70 donor units per week.

5.2 Reduction of alloimmunization: Therefore the general policy in transfusion of red cell and platelet concentrates must be to avoid immunization against leucocyte blood groups. The best method to reach this is the removal of leucocytes from the cell concentrates. Filtering of all the cell concentrates directly after production would be the most optimal procedure. This is not yet possible because of the high costs.

By a combination of buffy-coat removal, filtration of fresh erythrocyte concentrates only for a selected patient group (see later) and an improvement of the platelet production protocol, a major improvement can be reached for limited costs. The reasons for introduction of these modifications will be discussed.

5.2.1 Buffy coat removal: Removal of the buffy coat (containing 70% of the leucocytes) from each unit of blood will be the first step in diminishing the frequency of alloimmunization. This extra handling during processing can be easily implemented if the plasma/cell separation is automated as discussed. The advantages of buffy coat removal are:

i) an reduction of immunization against leucocyte alloantigens and thus less transfusion reactions.
ii) better quality of erythrocyte concentrates
iii) possibilities to improve platelet concentrates (see later)
iv) surplus of buffy coats can be transferred to BTS's which are in a constant shortage of platelet concentrates
v) reduction of viral load, if the viruses are leucocyte-related.
vi) an increase in plasma yieldof 65 ml per donation, when platelets are prepared

The increase in costs will be the price-difference between the different blood bag systems (triple versus quadruple bag, 1 pound per bag). Because of a lower percentage of transfusion reactions, a lower usage of platelet concentrates and an increased plasma yield this investment will decrease overall costs.
By transferring the surplus of buffy coats (30.000 in 1989 in East Anglia) to other centers an alternative source of income can be created.

5.2.2 Filtration of erythrocyte concentrates: In certain catogeries of patients (bone marrow transplantation candidates, polytransfusees, patients who do need long term platelet support, immunocompromized patients) alloimmunization against leucocyte bloodgroups should be avoided at all costs. The extra costs which have to be made once a patient is immunized are enormous (donor selection for platelet transfusions, selected plateletpheresis, increased frequency of platelet transfusions, treatment with high dose gammaglobulin). Alloimmunization against HLA class I alloantigens is also one of the reasons for unsatisfactory survival results in bonemarrow transplantation programmes and treatment of patients with haemato-oncological diseases because of fatal bleedings.
Removal of the leucocytes from fresh erythrocyte concentrates by filtration is an effective technique to avoid alloimmunization against HLA class I alloantigens.
At the moment bed-side filtration is fashionable in the East Anglia Region. This came into practice because of two reasons:

i) The BTS did not have the funds to provide this essential service
ii) Certain filter producers use very aggressive marketing techniques

It is questionable whether bed-side filtration is the most optimal form for leucocyte removal. On basis of scientific data there are more reasons to favor filtration of fresh erythrocyte concentrates:

i) Most of the alloantigen-bearing glycoproteins (e.g. HLA class I and II, FcRIII, GPIIb/IIIa, GPIb/IX) are shed into the preservative fluid during storage of non-filtered erythrocyte concentrates and these soluble glycoproteins are probably still immunogenic. Thus filtration of cell concentrates must be done directly after component production, when the concentration of these glycoproteins in solution is still at low.
ii) Filtration is a procedure which must be performed under strictly controlled conditions. As an example a too high flow rate during filtration will reduces the degree of the leucocyte removal. The personnel of the BTS are more aware of working with blood products according to standardized operating procedures (SOP's). Furthermore quality control as to the degree of leucocyte removal would take place in the BTS on a routine basis.
iii) Since sterile docking of plastic tubes is possible nowadays fresh units of erythrocyte concentrates can be filtered without affecting the outdating because of bacterial contamination. This will facilitate the logistics of providing filtered cell concentrates.

In conclusion filtration of erythrocyte concentrates is taking place in the East Anglia Region already. Thus the costs are made but the results are not optimal. On basis of the principal to optimize the quality of health care within the borders of restricted funding a relocate of the filtration procedure from bed-side to the BTS is advised. From experience on the continent we can conclude that about 10% of the total number of units have to be filtered. The budget needed for this 15 pounds per filtered unit. I request strong support from the RHA will trying to reshuffle funding from the distrct health authority level towards the BTS.

5.2.3 Leucocyte-poor platelet concentrates: Leucocyte-poor platelet concentrates (40x10(9) platelets/donorunit) can be prepared from buffy coats by standard centrifugations. This procedure does result in the lowest degree of leucocyte contamination (4-10x10(6) leucocytes/ donorunit) and the method is no more laborious than the one which is used at the moment in our BTS. Our production method is the preparation of platelet concentrates from platelet-rich plasma; in general this causes a much higher leucocyte contamination and a lower plasma yield. Furthermore the platelets have to be resuspended after the second hard spin which will decrease the functional capacities of the platelets. These platelet concentrates are filtered before transfusion to remove contaminating leucocytes (30 pounds/5 platelet concentrates).
In 1989 about 40.000 platelet concentrates were issued in the East Anglia Region; the percentage of these concentrates that were filtered is not yet known.
If the new platelet production method is introduced filtration will not be needed anymore and the degree of alloimmunization will decrease significantly. The investments needed to introduce this method are:

- training of personnel
- quadruple bags instead of triple bags
- devices for centrifuges

5.2.4 Pooling of platelet concentrates: Normally a patient is transfused with 5-6 platelet concentrates in one go. Pooling of platelet concentrates can be done before issuing the concentrate to the hospitals. Without pooling the infusion must be interrupted every 10-15 minutes, the spike has to be removed from the bloodbag and is reintroduced in the next one.
Pooling in the BTS can be done under sterile (sterile docking device). The conditions in the BTS will be standardized better. No extra equipment is needed and if the plasma/cell separation is automated probably no extra personnel will be needed either.

5.2.5 Irradiated blood: Two deaths from Graft Versus Host Disease (GVHD) has been reported in a pateint with a T cell lymphoma and a child with Hodgkin's diease, because no irradiated blood was available. Certain categories of patients must receive irradiated blood because of GVHD risks. Irradiation in the hospital by the radiotherapist is extremely coumbersome and is using extremely expensive equipment which should be dedicated to patient care only. With an increase in the intensive treatment of patients with malignant diseases of the blood irradiated blood must be available in the region.

5.3 Conclusion: In summary I advise the regional management to facilitate, by an increased funding of the BTS, the introduction of buffy-coat removal, the relocatian of the filtration procedure and to modify the platelet production procedure. These three changes are needed to minimiza the degree of alloimmunization. Prevention of alloimmunization will diminish the costs of transfusion therapy in the long term. Furthermore it is has been proven that the risk for transfer of viruses by bloodcell concentrates is greatly reduced by leukocyte-removal. In the immune compromised patient filtration is therefore a must in the future. A solution for irradiation of blood must be found.

I have to state that it will be difficult for me to bear the legal responsibility in a BTS which will not be capable of introducing these essential modifications. Although the modifications will require extra funding in the beginning, I am sure that everybody will agree that the patients have the right to be provided with blood-derived products produced according to the "State of the Art" in today's bloodbanking and that they are in this aspect supported in their legal rights by the "Consumer Protection Act 1987"..

6 Platelet support, a regional plan

6.1. Introduction: If a patient is alloimmunized (despite the suggested changes as outlined) and the survival of random donor platelets is decreased strongly (low increment values) donorselection is needed.
The following procedure is advised for the region:

i) Platelet crossmatch
A cross match with platelets from 20 random donors with a standard ELISA procedure can be used to select compatible donors. If the percentage of positive reactions is exceeding 70% selection on HLA class I phenotype is needed. A platetelet cross-match can be introduced only if leucocyte-poor platelet concentrates are prepared.

ii) HLA class I compatible
For this selection the number of HLA class I phenotyped donors must be increased. By a computer search the most compatible donor can be selected. Automation of the HLA typing will facilitate this (see later). With a cytapheresis 300-400x10(9) platelets can be harvested from the selected donor. These platelets should be filtered to remove the high percentage of contaminating leucocytes.

iii) Cryopreserved autologous platelets
Ongoing research in the field of cryobiology made it possible to cryopreserve platelets. Protocols for platelet cryopreservation are available, however there are no facilities in the centre for cryopreservation. This will be discussed more extensively in chapter 9.

7 Upgrading of immunohaematology

7.1 Introduction: New developments in immunohaematology have been partially realized. However with the lack of reagents budget and a budget for equipment a further improvement of the quality cannot be realized. The in-house production of erythrocyte typing reagents is consuming a lot of time. I advise the acquisition of commercial reagents when our own reagents do not meet National Standards. The expertise of Dr Voak's group is nationally and internationally recognized. An increase in the size of his group by starting a close cooperation with a commercial firm and the MRC groups could be realized.

7.2 Red cell phenotyping: There is a general consensus emerging that women in child bearing age should receive Rhesus and Kell compatible erythrocytes, to minimize the risk on the formation of irregular erythrocyte alloantibodies. A certain number of donors typed for all clinically relevant erythrocyte bloodgroups is needed to support alloimmunized patients in the region. The size of this donorpool has to be steadily increased during the coming years. Furthermore commercial reagents will be needed for phenotyping (see later).

7.3 Reagents for phenotyping: Bloodgrouping reagents will be replaced by monoclonal murine, rat or human antibodies. Thus the production of polyclonal typing reagents for our centre is not cost-effective. The quality will be lower than the commercial ones, the prize is higher and on ethical basis plasmapheresis of donors for specific antibodies will be restricted if monoclonal antibodies are available Monoclonal anti-A, anti-B, anti-AB and anti-Rh(D) are already used in our centre. Thus with an increasing usage of commercial reagents, our reagent department has to be minimized size.

7.4 Cell panels: Good cell panels which are needed for antibody identification cannot be provided to the region because there is no facility for long term storage of erythrocytes in our centre (see section on cryobiology). This means that a lot of time and reagents are used to find suitable donors for the fresh erythrocyte panels. Some of the regional hospitals are using commercial panels. The Addenbrookes does spend 10.000 pounds for its two cell panel on an annual basis. If cryobiology facilities are available high quality cell panels can be distributed to the hospitals for a competitive price.

7.5 Anti-D immuno-prophylaxis: Monoclonal antibodies against the Rh(D) antigen will be evaluated on their possible therapeutical application for immuno-prophylaxis by different research groups. If successful, the polyclonal anti-Rh(D) will be replaced by a blend of monoclonals. The volume of high titer anti-Rh(D) plasma needed will be strongly reduced. The plasmapheresis procedures to obtain specific plasma will not be necessary anymore. The timescale for this will be at least 5 years. I have started a cooperative research in this field with the group of Dr Nevin Hughes Jones (ARC, Babraham).

7.6 HLA/Lymphocyte phenotyping: There is a combined regional (platelet support), national and international (unrelated bone marrow transplant programme) wish to increase the number of complete (class I and II) HLA phenotyped donors. It is generally accepted that national cooperation in this field is needed since the size of donorpools is too big for a regional based organization. The activities of our centre are too limited. HLA phenotyping is laborious and therefore expensive. The capacity could be increased by automating oil-dispensing, dataprocessing and reading of LCT reactions.
To meet national and international requirements in terms of number of HLA phenotyped donors/region an extension of our activities is advised. We do have a relatively strong place in the HLA field since we are providing HLA typing reagents to different centers. In relation with our R&D plans in the field of monoclonal antibodies an increase in the activities in the HLA field could become profitable in the future.

7.7 Platelet serology: Platelet specific alloantigens can induce an immune response and cause refractoriness for platelet transfusions or post-transfusion purpura. Patients who are immunized against these alloantigens cannot be transfused further with platelets positive for the particular alloantigen. The development of platelet serology in the UK is far behind compared to the continent, excepting the centre of Prof Waters in London. Introduction of this technology is now possible because of my personal knowledge in this field and good working relation with the CLB of the NRC BTS in Amsterdam. A budget is needed to finance personnel, reagents and disposables. In the area of capital goods a fluorescence microscope is needed. For the cross matching facilities an ELISA reader and microplate centrifuges are required. Training of personnel in the CLB is advised .
Three groups of patients would benefit from the introduction of platelet serology:
haematolgy - problem solving in alloimmunized patients, selection of the optimal platelet donor
- diagnosis of Auto Immune Thrombocytopenia (the most frequent occurring non-malignant haematological disease)
paediatrics- alloimmunization in pregnancy/neonatal thrombocytopenia
The incidence of alloimmunization against platelet alloantigens in pregnancy is in 1:1000. This can result in the clinical picture of fetal or neonatal thrombocytopenia, which can be responsible for intracerebral bleeding and brain damage. Intrauterine, intracranial bleeding occurs in 10% of the alloimmunized cases. Good platelet serology will reduce the number of handicapped children and if an alloimmunized mother presents, optimal care can be organized in the succeeding pregnancies preventing intracerebral bleeds.

7.8 Polymerase chain reaction: The polymerase chain reaction (see section on virology) is a powerful tool in the detection of polymorphisms (bloodgroups). Because the method can be automated, PCR probably will be used in the more complicated phenotypings (like HLA).

7.9 Conclusion: In immunohaematology improvements are needed to give better patient care. This reshaping of the diagnostic department can be done for minimal extra costs if automation is introduced in the antenatal laboratory and if the Reagent laboratory is strongly reduced in size. Overall no extra personnel is needed in the diagnostic sector as outlined in the tables in chapter 11.

Chapter 8

8. New developments in virology

8.1 Introduction: The virological status of the donor demands our continued attention. Lessons have to be learned from the past in when ignorance of the risks of the transfer of viruses from donor to patient were underestimated. The first way is to continue in educating clinicians that blood is not the life-elixir (Blut ist eine wunderbares saft, sagte Faust zum Mephistoles) but that it can be very harmful indeed. Thus education on the usage of blood and blood products is an important task. The National Guide Lines for FFP and platelet use which are now in preparation by the BCSH Blood Transfusion Task Force will give us the crucial support in our wish to down regulate transfusion abuse.
Component preparation and supplying the patient only with that which he/she needs is a second step in the right direction. In the East Anglia Region 40% of the blood is still issued as whole blood. This should be reduced as discussed already to 0.05% at maximum. Removal of leucocytes and plasma will diminish viral load, also if artificial media for platelets are made available (probably in the coming two years) this should be introduced.
The abuse of fresh frozen plasma should be controlled and the plasma should be delivered to the BPL so that National plasma requirements can be reached and products can be prepared with a high safety in terms of viral status.

At the moment the implementation of the automated liquid handling system in the virology lab. is taking place and intergration with the main frame system is the next step to be made in improving the quality of our service.

8.2 New tests to be introduced:

8.2.1 ALT: ALT testing as a surrogate test on apheresis plasma (about 10% of our total volume) is needed because the BPL has agreed to work under a Cutter License for intravenous gammaglobulin production. This product is at the moment bought by the Hospital from commercial firms. The BPL will partially compensate for the testing, however their extra payments are not cost-effective. An increase in budget is required for ALT testing. In a letter from Dr Contreras our Division has suggested to BPL to acquire another license to avoid an increase in the number of donations which has to be screened for ALT. About 40% of the total plasma yield is needed to be self-sufficient.

8.2.2 HIV 2: From the first of April 1990 each donation should be investigated for antibodies against HIV2. It is at the moment not yet clear whether the test kits for the combined screening will have the same price as the old ones. Furthermore the positive reactions on repeat have now to be further investigated to determine whether the positive reaction is caused by antibodies against HIV1 or HIV2.

8.2.3 Hepatitis C: Although a decision on hepatitis C antibody screening has not yet been taken, it is likely that this screening has to be started before the end of 1990. However the advice from an expert committee is not yet released to the RTC's.

8.2.4 CMV testing: Certain categories of patients require CMV negative blood products. Because of the high incidence of CMV infection in the donor population a high number of donors have to be screened to provide a service for the issuing of CMV-negative blood products. At the moment the automated pipetting and the data processing for hepatitis B, HI and hepatitis C is introduced personnel will be available to increase CMV testing. Funds for acquiring reagents should be made available. Probably the Council of Europe will advise to provide filtered bloodproducts to patients who are CMV negative.

8.3 Polymerase Chain Reaction: The polymerase chain reaction is one of the most substantial advances in molecular genetics in the last decade. It is now possible to amplify specific DNA sequences - from as short as 50 base pairs to over 200 basepairs in length - more than a million fold in only a few hours. This gives the method an extraordinary power and sensitivity for the detection of minute amounts of viral contamination in blood products and blood derivates. This technique which is now fully automated for use in diagnostic laboratories, is in the hand of the QA officer a diagnostic tool which must be available.
Also in Immunhaematology and certainly in the R&D activities this method will be used (see there).

8.4 Conclusion: The extra funds needed for virology are considerable. With the increasing number of tests the time needed to inform the donors about the relative risks of having a positive test will increase exponentially. Therefore there is a need of a well trained counsellor.

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Page 1 of 37 pages (in 2 batches)

FROM: Dr. Willem Ouwehand.
Tel. GRO-C

Report attached as discussed.

C O N F I D E N T I A L

2nd Batch

Chapter 9

9. Cryobiology and tissue banking

9.1 Introduction: Cryopreservation (-196oC) of most blood cells (erythrocytes, platelets, lymphocytes, monocytes, bone marrow stem cells) and of different tissues (heart valves, tendons, bone) is possible. Development of tissue banking will be needed in the near future. Figures from the States show an exponential growth of tissue banking. In Europe centers for tissue cryopreservation are also sited within the BTS organization.

In the East Anglia Region storage of bone marrow cells has started on a small scale and requests have been made to actually start tissue banking (heart valves). Because of the activities of the MRC group of Dr. Pegg the level of knowledge in our area is outstanding. Implementation of cell cryopreservation in the BTS could be realized with their support.
Because of the major impact of the recombinant proteins (introduction of rec Factor VIII and rec Albumin) on the plasma-collection activities flexibility is important for the BTS organization. Tissue banking will fit in the organization without major modifications.

The reasons why such a new activity cannot yet be started are:
i) no equipment, ii) no funding and iii) no expertise.
If the BTS doesn't adopt these activities now, there is a big chance that the hospitals will start cryopreservation (like bone marrow preservation in the Addenbrooke's). A decentralized cryobiology service will be expensive and there is a risk of poor performance because of low levels of standardization.

Cryopreservation of bone marrow, platelets, heart valves can be started if funds are made available. A careful low profile initiation of this new activity would make us familiar with the overall problems connected with cryopreservation. If new possibilities emerge, such as endothelial cell seeding, pancreatic island cells transplantation, cellular cancer therapy, the centre will be capable of integrating these activities into an already existing organization matrix.

First attempts to investigate the possibilities for close cooperation with the MRC cryobiology group at the University of Cambridge (Dr. D Pegg) were extremely encouraging. A proposal to investigate the possibilities to incorparate the MRC cryobiology group in our centre has been send to Professor Carrell.

10. Humoral and cellular immunotherapy

10.1 Introduction: The new activities of the group of Dr Hale in the BTS will create a nucleus for the new R&D activities. It must be clear from the previous chapters that changes are needed for the BTS in the near future. It is not my intention to outline detailed research plans in this document. However some general new area's of transfusion related research will be discussed:

10.2.1 Antibody technology: The monoclonal antibody technology from the MRC groups is impressive. We will try to create research lines which are closely related with these groups and especially with Dr Waldmann's group.
Dr Winter's group has recently invented a technique to extract the genetic information from human B cells producing antibodies of potential therapeutical or diagnostic interest. These extracted genes are subsequently expressed in E. coli. Antibodies of diagnostic or therapeutic interest can be found during the routine immunohaematological and virology screening procedures which are taking place in our centre.
We will start with a well defined system, the Rh(D) antigen and the IgG alloantibodies against this antigen. This will fit in two main tasks of our centre: the antenatal Rh(D) immunoprophylaxis programme and the Rh(D) phenotyping of donor red cells. Cooperation with the group of Dr Hughes Jones (ARC, Babraham), who is already working on this subject, will be intensified.
If we are successful in using the immunoglobulin-gene-extraction model as described by Dr Winter's group, we could start some contract research with reagent producers. As mentioned already the expertise of Dr Voak is recognized far beyound the borders of our region and this will give us the possibility to contact interesting contract-research partners.

10.2.2 Activated killer cells: Some tumours are sensitive to cytokine activated killer cells (LAK cell therapy in melanoma and some kidney tumours). This concept of cancer cell killing is in active development and a combination of this approach with the antibody-mediated killing concept of Dr Waldmann will provide us with new anti-cancer treatment protocols. For this cellular therapy model cell-culturing facilities are needed. The possibilities for a low-profile setup of these facilities should be investigated.

10.2.3 Specific killer cells: T lymphocytes can be educated in the recognition of a specific target antigen. The T cell receptor is the trigger molecule for a powerful lytic machinery. Educated and antigen specific T cells can be proliferated in vitro. The question whether in vitro educated T cells can be used in humans cannot be answered yet. However, when the antigen-recognizing product of the B lymphocytes, the immunglobulin molecule can be reshaped and tailor-made, the antigen-recognizing part of the T cell, the T cell receptor will give us probably comparable opportunities. The organization at the genetic level which is at the basis of the variability in antigen recognition of the immunoglobulin molecule and the T cell receptor molecule does show a high degree of homology.
Thus educated T cells will be probably used in the future for the killing of viral infected cells and other cells causing disease (e.g. autoreactive cells). Cryopreservation of killer cells of certain HLA phenotypes and a predefined specificity and the in vitro expansion of these cells will give us the tools to remove certain unwanted cell subsets from the human body.

Chapter 11

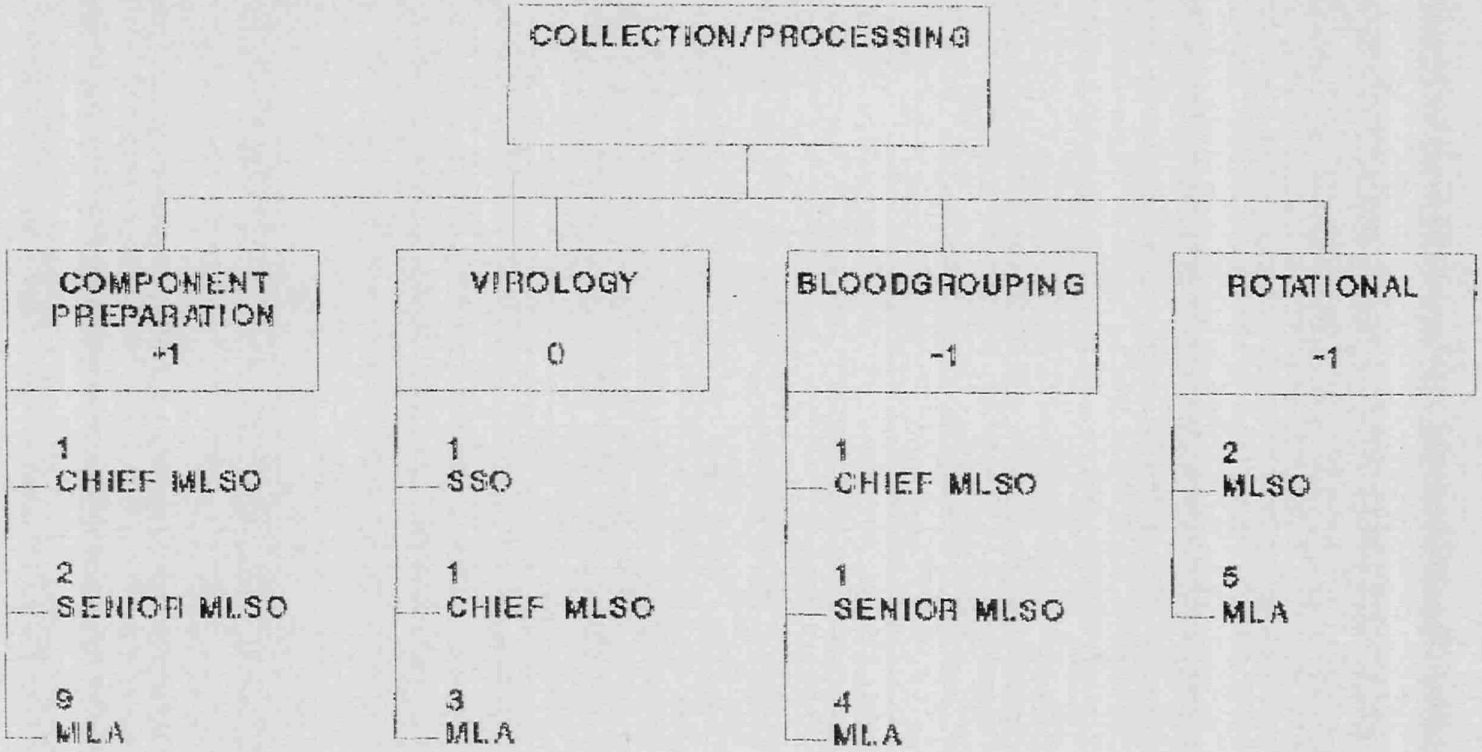
11.Personnel

11.1 Introduction: The grade of training of personnel is to low and is restricting the flexibility of the organization. One of the major disadvantages of the personnel management is the high degree of rotation of staff on regular basis from one department to another. This blocks the possibility to create expertise. This means that many responsibilities are still in the hands of senior-staff which restricts them to work on education and training. This vicious circle has to be broken and I have experienced the model of a well trained staff and I am sure it will improve the quality of health care, not in the latest because the staff will be motivated by the increase in responsibilities.

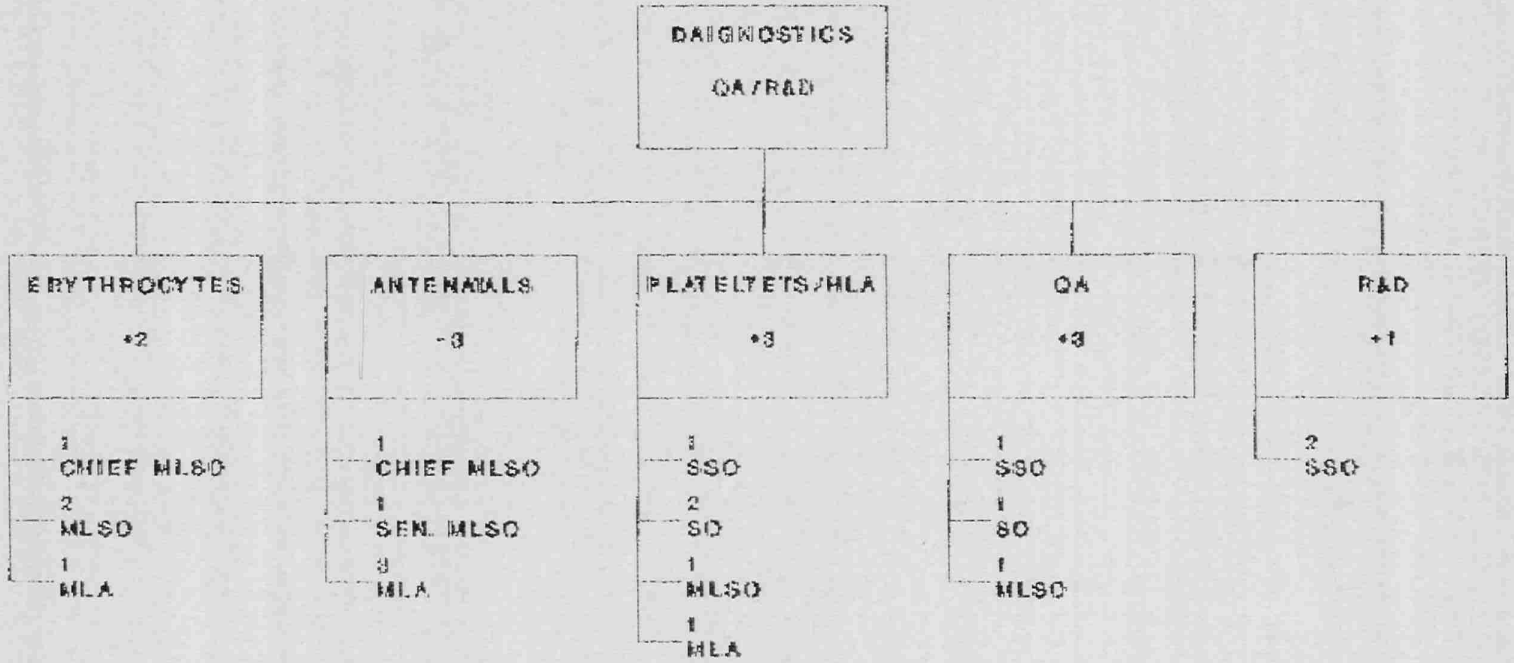
The question whether the centre is still capable to attract good personnel is a problem of major concern. The fact that our pay scales are not competitive with those of the commercial sector is only adding to the problem of personnel recruitment.
I propose to further refine the personnel management structure in the laboratory sector. The staff working in the blood component production, virology and bloodgrouping laboratories can be on MLA level, supervised by a senior and a chief MLSO.
The personnel in the more specialised laboratories (antenatal, erythrocytes, HLA/platelets, R&D and QA) needs a higher level of training (SSO and SO) to be capable to react on new developments in transfusion medicine.

Conclusion: The personnel management must be optimized and higher degree of differentiation in scales is needed. A suggestion for a restructuring is shown in the two tables.

PERSONNEL



PERSONNEL



proposed reorganization of the staff of
the diagnostic and the production labs

	sso		so		chief mlso		sen. mlso		mlso		mla		total	
erythrocytes	0	0	0	0	1	1	0	0	1	2	0	1	2	4
antenatal	0	0	0	0	1	1	1	1	1	0	5	3	8	5
plat/hla	1	1	0	2	0	0	0	0	0	1	1	1	2	5
qa	0	1	0	1	0	0	0	0	0	1	0	0	0	3
reagents	0	0	0	0	1	0	1	0	2	0	3	0	7	0
R&D	1	2	0	0	0	0	0	0	0	0	0	0	1	2
total	2	4	0	3	3	2	2	1	4	4	9	5	20	19
+/-	+2		+3		-1		-1		0		-4		-1	

	sso		so		chief mlso		sen. mlso		mlso		mla		total staff	
bloodgrouping	0	0	0	0	1	1	2	1	1	0	3	4	7	6
virology	0	1	0	0	1	0	2	1	2	0	0	3	5	5
blood product	0	0	0	0	1	1	2	2	2	0	6	9	11	12
rotational	0	0	0	0	0	0	1	0	3	2	4	5	8	7
total	0	1	0	0	3	2	7	4	8	2	13	21	31	30
+/-	+1		0		-1		-3		-6		+8		0	
grand total	2	5	0	3	6	4	9	5	12	6	22	26	51	49
+/-	+3		+3		-2		-4		-6		+4		-2	

Chapter 12

12. Training and education

12.1 Introduction: The field of Transfusion Medicine is changing like most of the areas of medical care. This means a continuous process of adaptation. Therefore funds should be available for training and education of our staff and our Regional colleagues.

12.2 Training of staff: One of the reasons why the attitude towards new developments is in general not very positive, is because the personnel is not aware of the major alterations which must take place. "Education permanente" is the only way to facilitate the process of continuous alterations and is a major tool to protect the BTS from a rigid structure. Because of our close integration with the University we do have the possibility to stimulate educational programmes and we at least should be able to participate in the important National meetings. The senior staff should have funds available to visit other centres and the important International Meetings.
This will help us in the future to minimize mistakes in the planning of new developments and it will give us the opportunity to introduce new techniques which have been developed by other groups. The reinventing of the wheel on costs of the Regional Budget is partially related with the restricted possibilities to exchange knowledge with colleagues in the UK and abroad.

12.3 Education in the Region: Training and education in Transfusion Medicine for the Region is a task for the RTC. At the moment the relation with the consultant haematologists is minimal. Therefore our influence on the (ab)use of blood products is limited. Our attitude of not being service-minded has reduced our ability to down regulate the use of blood products.
In my first contacts with the regional haematologists, it was clear that there is a wish for Regional training activities for transfusion-laboratory personnel and for educational seminars for haematologist and anesthesiologists.
The restricted budget for education and training won't support our idea that education of our clients is the only way for influencing the use of blood products.

12.4 Audit on blood product usage: The bloodtransfusion policy in the Regional Hospitals is an important subject for an audit. To organise this the BTS needs to investigate the reasons for transfusing blood. Therefore we should like to receive financial support from the funds allocated for this purpose. The first audit on this issue could help us to come to the formation of "Hospital Transfusion Committees" which could help us in optimizing the use of bloodproducts in our region.

Chapter 13

13. The managerial structure

13.1 Introduction: On a historical basis the managerial structure is rather hierarchical. To be capable to cope with the major alterations which will take place in the BTS in the coming years another organizational structure has to be defined. In this new structure the communication between the different members of the management team must be optimized, so that we can react adequately and quickly on the changing profile of the services we must deliver to the region. The organization must be open-minded towards alterations and and we must realize that by optimizing our service is the only way to keep our future clients in a competing health market. This implies that quick and smooth communication lines are required througout the organization and that there is open-door policy in the management team. The interaction with other centers and the BPL can be intensified. The Cambridge University and Academic Transfusion Centers abroad can be used as a reservoir for innovative ideas.
For the interregnum the formation of a triumvirate is advised which is formed by Dr. Blagdon, Mr Hawdon and Dr. Ouwehand. One of them should have the overall responsibility. The tasks in this triumvirate will be divided. Some organograms are included to outline the new management structure.

13.2 Interaction between management and staff: The influence from the management team on the organization can be improved by decreasing the distance between management and staff. In this more meritocratical model the overall responsibilities of the staff will be increased which will be accompanied with an intensification of training and education and a reduction of staff rotation. The role of the QA officer in setting the standards for training and education is of crucial importance.

13.3 The laboratory structure: The number of sublaboratories in diagnostic sector is too high. The laboratory structure should be based on concentration of expertise. In the organograms the general outline for a better laboratory organization model is given.
There is a clear cut difference between the laboratories, which are directly related with the process of blood component preparation (component preparation, bloodgrouping, virology and issues) and the diagnostic, QA and R&D laboratories. The latest three will establish a high degree of interaction with the synthetic peptide group of Dr Hale the monoclonal antibody research group of Prof Nevin Hughes Jones (ARC, Babraham) and the cryobiology group of Dr Pegg.

Chapter 14

14. Quality assurance

14.1 Introduction: The QA department has to expand as planned, because standard QA procedures are not performed routinely. Our platelet preparation might serve as an example. The number of platelets, the volume of plasma wherein the platelets are suspended and the degree of leukocyte and erythrocyte contamination per unit are not known. Thus basic information which should be available for the clinician to evaluate therapy is thus not available. The storage temperature of the platelets is not according to regulations.
Not enough equipment is available to monitor these parameters, which brings the QA officer in a difficult situation in which he has to accept that products are released which may fail to meet accepted requirements.
The QA officer can play an important role in cost savings by advising in the removal of unnecessary services/procedures and to increase the ability to "get it right first time" when new procedures are introduced.

To ensure that the need for Quality is understood by all personnel, the QA officer must be guaranteed that he can influence the training and education programme. By giving him the responsibility over the these programmes is the most direct way to reach this target. By intergrating his laboratories with the R&D ones, he will find a reservoir of knowledge, which will help him in optimizing the training programme.

Chapter 15

15. The premises

14.1 Introduction: The premises are adequate in space and there is enough space for new developments. The laboratories on the first floor F wing are however not equipped according to today's standards. The wooden benches are not adequate for the job anymore and are not acceptable in a modern BTS where high hygiene standards are imperative. These laboratories should be upgraded in the coming two years and funds should be made available. I realize that this will need extra investments, however it is generally counter-productive and unsatisfactory to provide highly trained personnel with suboptimal facilities. At the moment I cannot start my R&D work on site, because of the poor laboratory outfit, which means that 50% of my time I am not working in the BTS premises.

With respect to future developments it would be advantageous to shift away from the concept of small separate laboratories, tailor made for groups of two or three persons. More spacious laboratories will adopt to changing specifications more easily.
I am sure that a high flexibility in the laboratory space reduces the need for future investments and it will guarantee quick and easy adaptation to new developments.

16.2 Disposables/reagents/chemicals: The extra funds to finance disposables, reagents and chemicals are essential. To reduce the labour-intensive recycling and autoclaving of glass work and to meet hygiene standards disposables are needed. The reagent problem is of major concern. Diagnostic tests are performed with outdated reagents, there is a continuous shortage of good typing reagents for erythrocyte phenotyping and there are no reagents for standard platelet serology. Often tests are performed according to old-fashioned methods because standard modern disposables are not available. If the cryobiology facilities are funded the centre could issue screening panels of a good quality for the region. At the moment most hospitals are buying commercial panels (the Addenbrookes spent/year about 10.000 pounds for this). Thus the supply of identification panels to the region would finance assist in the capital-investment needed for cryobiology.

16.3 Personnel and miscallaneous: The extra personnel is needed to establish the quality control procedures, to improve the donor/BTS relation, to recruit financial expertise and to supply counselling service for these donors who are not accepted for donation. If the reorganization of the diagnostic and the production departments can be realized, than the QA staff can be recruited from already available positions. The wish to have a financial expert in our team is directly related with the planned cross-charging with the hospitals in 1991. The miscalleneous post is partially needed to finance an intensification of the training and education programme and is the flexibility needed in the R&D budget to finance all sorts of smaller laboratory items.

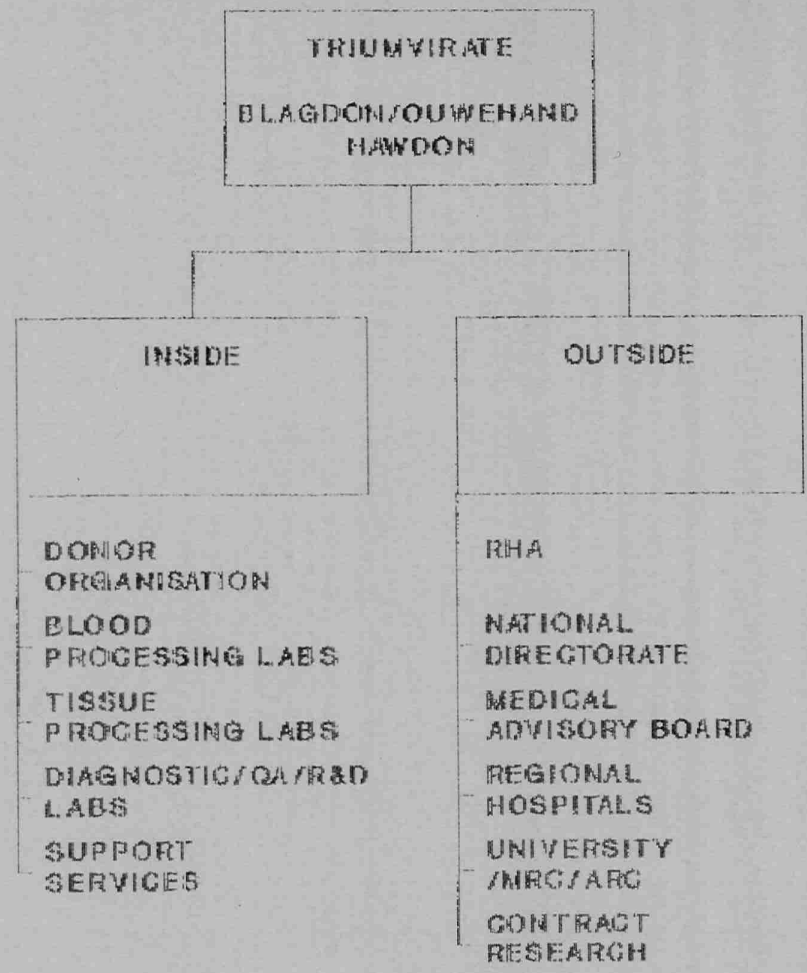
16.4 The liver transplant dilemma: The average costs for the overall bloodproducts in a liver transplant patients is about 2.900 pounds. This programme continues to expand, with 95 transplants in 1989 comparted with 83 in 1988. Analysis of a 4 month period in '989 showed that the liver transplant programme used 3% of all red cells produced in the region, plus 9,5% of all platelets produced and considerable amounts of FFP, cryoprecipitate and albumin. Provision for some support is made in that the health region from which the NHS patients originate can be asked to supply blood products, which are not cross charged. However this may not always be available and 33% of patients transplanted in the Addenbrookes are either overseas private patients or from the EEC. Three of these patitents had to be provided in december 1989 and the toal costs were 10.000 pounds.
There is not enough compensation for this service, although considerable central funds have been made available to finance the liver transplants in the Addenbrookes. Attempts should be made by the RHA and the BTS to get extra funding for this activity, because it affects to much our other service tasks.

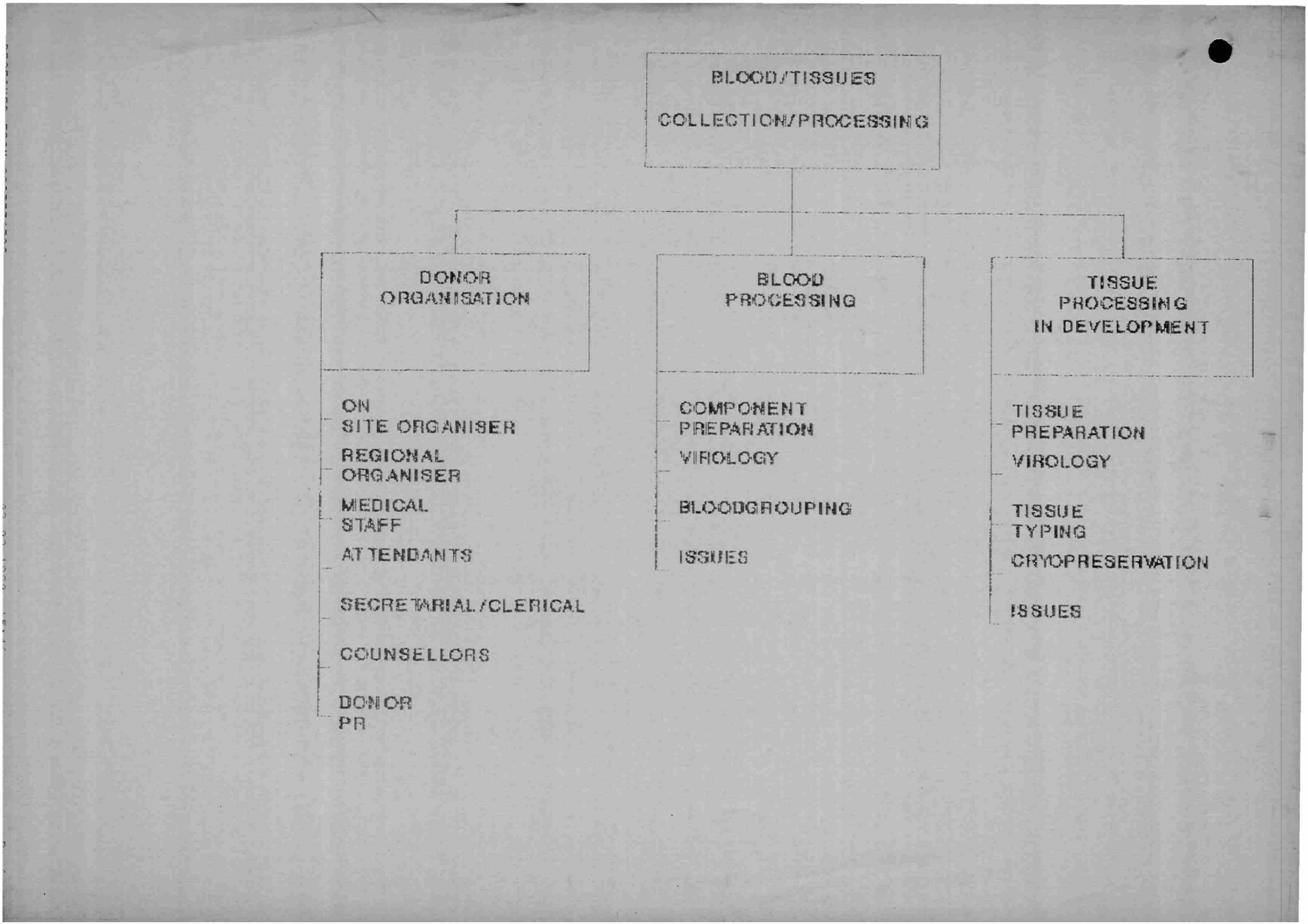
INVESTMENTS FOR THE EAST ANGLIA BLOOD TRANSFUSION SERVICE 1990-1993

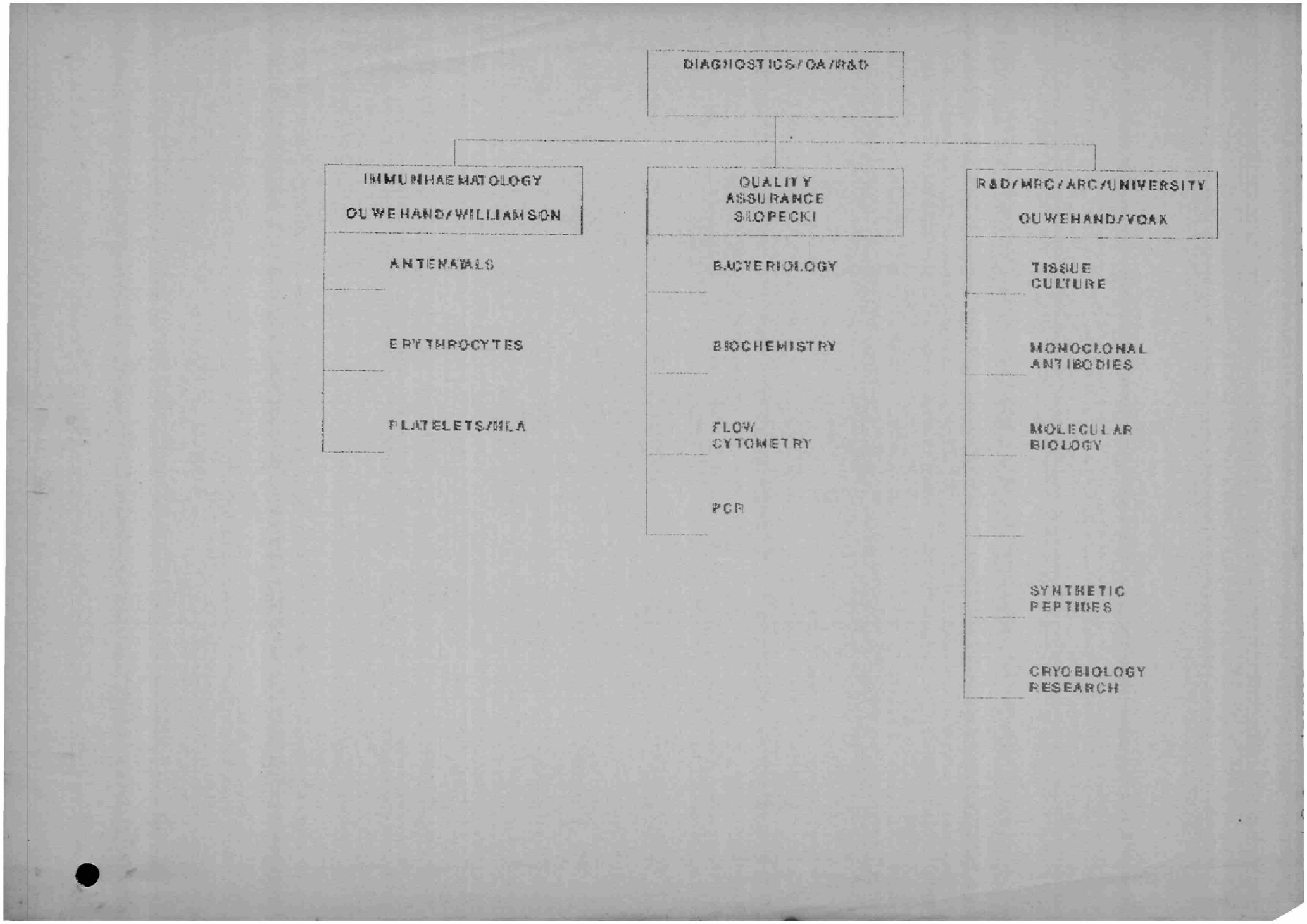
	price/ piece	nuu- ber	replac capital goods	new capital goods	mainte- nance	national regula- tions	dispo- sables	rea- gents	chemi- cals	person- nel	miscal- laneous
chapter 3											
personal computers	4	12	12	36							
computer hard ware antenatal	20	1		20							
pipetting machine antenatals	30	1		30							
automation HLA reading	10	1		10							
automation component prep.	20	4		80							
chapter 4											
session disposables/arm	0,0003	90000					27				
crates, coolingdevices/units	0,065	400		26							5
increase nr.plasmapheresis							2			2	
trolleys	0,1	40		4							
blast freezers	15	3		45							
high speed centrifuges	10	6	60								
increase plasma storage	1,5	4		6							
reagents bloodgrouping						53					
chapter 5											
different bloodbags	0,001	90000					9				
filtration	15	9000					135				
irradiator	50	1		50							
chapter 6											
elisa reader	5	1		5							
fluorescence microscope	10	1		30							
centrifuges	8	3	24								
cooled centrifuge	10	1		10							
reagents							5	3			
disposables							5				
chapter 7											
freezer	1	1		1							
fridge	0,5	1		0,5							
centrifuges	8	3	24								
cell panels								10			
reagents	6							6			
disposables							5				
chapter 8											
hepatite C						200					
ALT						16					
HIV 2						20					
counselling										25	
Chapter 9											
cryobiology tanks	6,2	3		18,6							
computerized cooling device	6,6	2		13,2							
liquid nitrogen storage	0,3	10		3							
liquid nitrogen /day	0,015	365							5,5		
laminar flow hood				20							

lab refurbishment				10								
disposables												
reagents							8	4	4			
chemicals												
chapter 10												
general equipment needed to												
start R&D work				60								
laminar flow hood				20								
cell incubators				15								
centrifuges				15								
-70oC				9								
incubators				15								
fume cupboard				10								
waterbath				8								
reagents								12				
chemicals									4			
disposables							18					
miscellaneous											10	
chapter 12											10	
chapter 13												
financial expert										20		
chapter 14												
aggregometer				10								
cell counter				20								
PCR instrument				9								
FACS flow cytometer				70								
reagents								6				
disposables							6					
1 BSO, 1 SO, 1 MLA										30		
chapter 15												
laboratories F wing						95						
air conditiong production				20								
electrical supply						41						
transport						70						
total			120	694.3	206	291	220	41	13.9	77	25	

MANAGEMENT TEAM







SUPPORT SERVICES

COMPUTERS

HEALTH AND SAFETY

ADMINISTRATION

SECRETARIAL

FINANCIAL

SUPPLIES

CLEANING

MAINTENACE

TRANSPORT